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ETS AND
LUNG CANCER IN NONSMOKERS

VOLUME II

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THIS ISSUE BINDER IS INTENDED TO PROVIDE A BASIC, COMPREHENSIVE REVIEW OF THE SCIENTIFIC LITERATURE REGARDING A SPECIFIC TOPIC ON ETS AND THE HEALTH OF NONSMOKERS.

PRIMARY STUDIES AND REVIEWS HAVE BEEN HIGHLIGHTED TO IDENTIFY (1) USEFUL OR HELPFUL INFORMATION (YELLOW HIGHLIGHT) AND (2) ADVERSE RESULTS OR OPINIONS (BLUE HIGHLIGHT).

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CRITICISMS OF THE EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Some general criticisms are applicable to the majority of the epidemiologic studies on ETS and lung cancer.

Strength of the association

- Wynder and Kabat wrote in 1990:

  > An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer.[1]

  Such a weak association calls for special attention to possible sources of bias and confounding.

Exposure bias

- Spouses, next-of-kin or friends are sometimes asked to estimate the amount of ETS to which they think the subject was exposed. This may result in something called "exposure bias" or "exposure misclassification."[2]

- Exposure indices and risk estimates based on this type of information may be improper and incorrect.

- One example of this was reported in the Garfinkel, et al., study, published in 1985, which reported relative risks of 0.83 when the cases answered questions about ETS, 0.77 when

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the cases' husbands answered, and 3.57 when the cases' children answered (a copy of this study may be found in Section A of this notebook).

Reporting bias

- Another type of bias that may arise is "reporting bias," which may result if cases and controls respond differently to questions about personal smoking and ETS exposure.[2]

Publication bias

- "Publication bias" arises from the apparent failure by scientific journals to publish papers reporting negative or weakly positive results. If this occurs, the set of published investigations may not be truly representative of all the studies in the area.[3]

Confounding factors

- The studies did not always account for possible confounding factors. (This is addressed in more detail in the section in this notebook on confounders.)

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Use of questionnaires

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.[4] Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure.

- Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.[5]

Histology

- Lung cancer diagnoses were not always histologically or pathologically verified.[1]

- Also, the histological composition, i.e., the type of lung cancer, differed among studies (in some studies, all histological types were included; in others, some types were excluded).[1]

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"Data-dredging"

- Investigators often examine numerous subgroups of the study population, and may report only those conclusions which fit with their hypothesis.[1] (This is sometimes called "data-dredging.")

Misclassification

- If the personal smoking status of subjects is not accurately classified, it could result in "misclassification bias."

- One critic, Peter Lee, contends that the reported "risks" for nonsmokers are the result of bias caused by a small number of smokers who are reported in the studies as nonsmokers.[6]

Conclusion

German scientist Karl Überla discussed some criticisms of the ETS-lung cancer studies at a recent scientific symposium in Argentina:

> The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biological

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plausibility can be judged controversially.[7]

The eminent statistician Nathan Mantel concluded the following:

> [I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith.[3]

Copies of critical papers, highlighted in yellow for useful information and in blue for adverse statments, are found at Tabs 1-7.

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CRITICISMS OF THE HIRAYAMA STUDY

Numerous criticisms of the Hirayama study have been made.[8-21] They include:

- The age distribution of the sample is not representative of the total Japanese population, particularly for women over the age of 40.[8] When a statistical correction is made for this bias, the increased relative risk reported by Hirayama virtually disappears.

- The appropriateness of Hirayama's standardization of the data by husband's age, rather than by subject's, has been questioned.[9-12] When Kilpatrick re-analyzed the data adjusted by subject's age, the model used by Hirayama was shown to be inappropriate and the reported significantly elevated risk associated with husband's smoking was no longer apparent.

- The Hirayama study was not designed to investigate ETS exposure; it is inappropriate to use it to make conclusions about the hypothesis of an ETS-lung cancer relationship.[8]

- Errors and internal inconsistencies in the data and in risk ratios and confidence intervals have been noted and publicly acknowledged by Hirayama.[13-15]

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- The design of the study has been criticized, e.g., use of death certificates as evidence for lung cancer is unreliable[8]; autopsy or histology results were available for only 11.5% (23 of 200) of the cases[8,16]; use of the smoking status of the subject's husband as a surrogate measure for ETS exposure is not reliable[8,12]; many possible confounding factors were overlooked.[8,17]

It appears that Hirayama has never adequately addressed the criticisms; for instance, his 1990 monograph on the study persists in presenting the same data analyses that have been particularly criticized.[18] In addition, Hirayama has not made his original data available for review.[8,19,20]

A bibliography of the criticisms follows. Copies of selected papers are given at Tabs 8-20. They are highlighted in yellow for useful information and in blue for adverse statements.

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CRITICISMS OF THE TRICHOPOULOS STUDY

Regarding the Trichopoulos, et al., study, the following criticisms have been made:

- In 1990, Letzel and Überla evaluated the quality of ETS-lung cancer studies.[22] Based on possible sources of bias and other problems with study design, they concluded that the Trichopoulos, et al. study, in particular, is "methodologically unacceptable" and is "a textbook example of how a case-control study should not be performed." Furthermore, they reported that this study may strongly influence the outcomes of meta-analyses of the ETS-lung cancer epidemiological studies (e.g., when the Trichopoulos study was included in meta-analyses of all possible case-control study combinations, it appeared in 330 of the 353 significant study combinations).

- Methodologically, the study has been criticized for selecting cases and controls from different hospitals; for excluding patients with adenocarcinoma and with alveolar carcinoma; for the lack of histological or cytological confirmation in 35% of the cases; and for its small sample size.[8,24] According to Überla, the small sample size means that "the statistically 'significant' results of this study may well be artefacts from chance, bias or confounding."[23]

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Copies of the articles referenced above, highlighted in yellow for useful information and in blue for adverse statements are found at Tabs 21-23.

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REFERENCES
General Criticisms

1. Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.

2. Kilpatrick, S.J., "Misclassification of Environmental Tobacco Smoke Exposure: Its Potential Influence of Studies of Environmental Tobacco Smoke and Lung Cancer," Toxicology Letters 35: 163-168, 1987.

3. Mantel, N., "Lung Cancer and Passive Smoking," British Medical Journal 294: 440, 1987.

   Newcombe, R., "Towards a Reduction in Publication Bias," British Medical Journal 295: 656-659, 1987.

4. Coultas, D.B., Peake, G.T. and Samet, J.M., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," American Journal of Epidemiology 130(2): 338-347, 1989.

   Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," American Journal of Public Health 80(8): 988-990, 1990.

5. Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," American Review of Respiratory Disease 142: 602-606, 1990.

6. Lee, P.N., "Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?" Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 25-36.

7. Überla, K., "Epidemiology: Its Scope and Limitations for Indoor Air Quality," Indoor Air Quality (Buenos Aires: National Academy of Sciences of Buenos Aires, Argentina, 1988): 45-60.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

REFERENCES
Criticisms of Hirayama, 1981

8. Überla, K. and Ahlborn, W., "Passive Smoking and Lung Cancer: A Reanalysis of Hirayama's Data," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 333-340.

9. MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 915-916, 1981.

   MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465, 1981.

10. Lee, P., "Passive Smoking," Food Chemistry and Toxicology 20: 223-229, 1982.

11. Kilpatrick, S. and Viren, J., "Age as a Modifying Factor in the Association Between Lung Cancer in Non-Smoking Women and Their Husbands' Smoking Status," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 195-202.

12. Kilpatrick, S., "An Example of Extra-Poisson Variation Suggesting an Under-Specified Model," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 83-90.

    Kilpatrick, S., "Model Specification Effects in ETS/Nutrition Research," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 257-271.

13. Lee, P., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465-1466, 1981.

14. Hirayama, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1466, 1981.

15. Layard, M. and Viren, J., "Assessing the Validity of a Japanese Cohort Study," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 177-180.

16. Grundmann, E., Miller, K.-M. and Winter, K.D., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.

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17. Sterling, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.

18. Hirayama, T., Life-Style and Mortality: A Large-Scale Census-Based Cohort Study in Japan, (Basel: Karger, 1990).

19. Adlkofer, F., "Probleme mit dem Passivrauchen (The Problems of Passive Smoking)," Der Kassenarzt 27(51/52): 29-39, 1987. Translation.

20. Ahlborn, W. and Überla, K., "Passive Smoking and Lung Cancer: Reanalyses of Hirayama's Data," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 169-178.

21. Aviado, D., "Toxicological Basis for Regulation of Indoor Air Quality," Journal of Applied Toxicology 8(3): 155-157, 1988.

Diamond, G. and Forrester, J., "Clinical Trials and Statistical Verdicts: Probable Grounds for Appeal," Annals of Internal Medicine 98(3): 385-394, 1983.

Gostomzyk, G., "Krank durch Passivrauchen (Disease Due to Passive Smoking?)," Munch med Wschr 124(4):16, 1982. Translation.

Kornegay, H. and Kastenbaum, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914, 1981.

Mantel, N., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914-915, 1981.

Mantel, N., "Epidemiologic Investigations: Care in Conduct, Care in Analysis, and Care in Reporting," Journal of Cancer Research and Clinical Oncology 105: 113-116, 1983.

Rutsch, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 985, 1981.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

REFERENCES
Criticisms of Trichopoulos, et al., 1981

22. Letzel, H. and K. Überla, "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.

23. Überla, K., "Lung Cancer from Passive Smoking: Hypothesis or Convincing Evidence?," International Archives of Occupational and Environmental Health 59: 421-437, 1987.

24. Heller, W.-D., "Lung Cancer and Passive Smoking," The Lancet II: 1309, 1983.

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Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment*

E. L. Wynder and G. C. Kabat

Summary

The possibility that exposure to environmental tobacco smoke (ETS) may increase the lung cancer risk of nonsmokers has become a cause of public concern. It is unknown whether the levels of carcinogens in the diluted sidestream smoke of tobacco products that reach the nonsmoker's lung are sufficient to induce cancer. Available epidemiologic studies suggest a slight increase in the relative risk of lung cancer in nonsmokers due to exposure to ETS created by a smoking spouse. However, not all studies have found a significant association. The epidemiologic studies are examined in the light of the criteria of judgment of causality, including strength of association, consistency, temporality, methodological issues, and biological plausibility. Suggestions for further research, including studies in high-exposure populations and greater attention to histology, are proposed.

Introduction

Epidemiologists, chemists, biologists, physiologists, physicians, and public health officials have given much attention to the association of environmental tobacco smoke (ETS) exposure and the development of lung cancer in nonsmokers. A biological basis for such an association clearly exists because smoke constituents demonstrated to be carcinogenic in laboratory animals are inhaled and retained by the nonsmoker. Metabolites of tobacco-specific smoke constituents have been identified in the saliva, blood, and urine of nonsmokers after exposure to ETS (Greenberg et al. 1984; Hoffmann et al. 1984; National Academy of Sciences 1986; USDHHS 1987; Sepkovic et al. 1988). Several epidemiological studies have found a positive association between ETS exposure – usually defined as being due to a smoking spouse – and lung cancer (Hirayama 1981; Trichopoulos et al. 1981; Correa et al. 1983; Sandler et al. 1985; Garfinkel et al. 1985; Akiba et al. 1986; Dalager et al. 1986; Pershagen et al. 1987). Other studies have found no significant association (Garfinkel 1981; Chan and Fung 1982; Koo et al. 1983; Kabat and Wynder 1984; Wu et al. 1985; Lee et al. 1986). No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

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The epidemiological study of weak associations is burdened with problems that may yield artifactual positive findings or may show negative findings where a real association exists. The association of ETS and lung cancer risk, even if weak, would still be of concern as a public health problem in that most people are at one time or another exposed to smoke from burning tobacco products and the exhaled pollutants of tobacco smokers. A weak association in epidemiology requires careful examination and an understanding of the variables in question and all of the factors influencing the association (Wynder 1987).

In this overview we critically examine the published studies on ETS exposure and lung cancer to determine whether the evidence presented to date permits a sound conclusion as to causation.

General Exposure to ETS

At the outset we need to emphasize that an association between ETS and lung cancer must be deemed possible. A recent survey of self-reported exposure in a hospitalized population revealed that 66% of men and 60% of women had ETS exposure in childhood; 32% of the men and 61% of the women reported ETS exposure in the home in adulthood; and 60% of the men and 62% of the women who worked outside the home reported ETS exposure at work (Kabat and Wynder, unpublished data, 1987).

Critical Assessment

The first Surgeon-General's Report on Smoking and Health, published in 1964 (USPHS 1964), clearly delineated the criteria of judgment for causality. These criteria included: the magnitude of the association, consistency, temporality, and biological plausibility. Since these criteria were considered necessary to prove causation for a strong association, namely, active smoking and lung cancer, they should be equally required to determine the causality of weak associations (Wynder 1987). Let us examine the epidemiological evidence linking ETS with lung cancer in respect to these criteria.

Strength of the Association

An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer (Table 1). If the observed relative risk is small, it is important to determine whether the effect could be due to biased selection of subjects, confounding, biased reporting, or anomalies of particular subgroups.

Consistency

If an association is real, internal consistency should be apparent within and between different studies. The majority, but not all of the studies of ETS and lung cancer have shown a positive association for ETS-exposure due to a smoking spouse (Table 1). In most of the studies, the confidence interval includes 1.0. While the prospective study by Hirayama (1981a) among Japanese women showed a significant association with the husband's smoking (largely adenocarcinomas), the prospective study among American

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Table 1. Summary of results of studies relating lung cancer risk in married women to their husbands' smoking habits

	Relative risk	95% Confidence interval
Prospective studies		
Hirayama (1981)	1.63	1.25–2.11
Garfinkel (1981)	1.18	0.90–1.54
Case-control studies		
Trichopoulos et al. (1981)	2.1	1.18–3.78
Chan & Fung (1982)	0.75	0.44–1.30
Correa et al. (1983)	2.03	0.83–5.03
Koo et al. (1983)	1.54	0.90–2.64
Kabat & Wynder (1984)	0.79	0.26–2.43
Wu et al. (1985)	1.2	0.6 –2.5
Garfinkel et al. (1985)	1.12	0.74–1.69
Lee et al. (1985)	1.03	0.41–2.47
Akiba et al. (1986)	1.48	0.88–2.50
Pershagen et al. (1987)	1.28	0.75–2.16

Table 2. Distribution of lung cancer by histologic groups in smokers and never-smokers. (From Kabat and Wynder 1984)

	Smokers		Never-smokers	
	Males (N = 1882) [%]	Females (N = 652) [%]	Males (N = 37) [%]	Females (N = 97) [%]
Kreyberg I	63	52	35	21
Kreyberg II	32	43	54	74
Mixed and undifferentiated/anaplastic	5	5	11	5

women by Garfinkel (1981) did not. It has been suggested that Japanese and American women are exposed to different levels of ETS due to different conditions in the two countries. Such differences could account for this disparity (Hirayama 1981b).

Within those studies presenting specific histologic analysis, differences exist in respect to the type of lung cancer involved. In active smokers, tobacco smoke exposure has a causative effect predominantly on squamous and small cell types of lung cancer (Kreyberg I), with a lesser, though still significant causative effect on the glandular type (Kreyberg II) (Wynder and Stellman 1977). Among nonsmokers, however, the glandular type of lung cancer predominates among both men and women (Kabat and Wynder 1984) (Table 2). The effect of ETS would thus be expected to be primarily responsible for the higher rate of adenocarcinomas among nonsmokers. The studies by Dalager et al. (1986) and Pershagen et al. (1987), however, suggest that the effect of ETS exposure is limited to induction of squamous cell lung cancer (Table 3). If this were, in fact, the case, then only the squamous or small cell type of lung cancer in nonsmokers

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Table 3. Histology-specific odds ratios for spouse smoking from two studies

Study	Histologic type	N	Odds ratio	95% C.I.
Dalager et al. (1986)	Adenocarcinoma	16	1.02*	0.33– 3.16
	Squamous & Small Cell Ca.	14	2.88*	0.91– 9.10
	Other	18	1.31*	0.48– 3.57
Pershagen et al. (1987)	Squamous or Small Cell Ca.	20	3.3	1.1 –11.4
	Other	47	0.8	0.4 – 1.5

would be affected by ETS. Clearly, it is important that investigations of the effect of ETS exposure on lung cancer development in nonsmokers take histology into account, so as to determine whether an effect of ETS is limited to certain histological types.

Since smoking is more prevalent in lower income groups, at least among men, lung cancer in nonsmoking women in these groups should have a higher incidence. Thus, the influence of the level of education on smoking habits in the examined population needs to be considered as a possible confounder. Few studies to date have done this.

Methodological Issues

A particular concern in weak associations is reporting bias, that is, potentially differential reporting of exposures between cases and controls. In terms of ETS, does the lung cancer patient report exposure to tobacco smoke, be it at work, at home, at social functions, in childhood or adulthood, differently than the control? The case is likely to have a different attitude toward this question than does the control, a handicap not applicable to prospective studies. It needs to be determined whether the case's attitude towards questions on ETS exposure leads to under- or overreporting. Cases are likely to underreport their own smoking (Lee 1987), and they may tend to overreport their exposure to ETS and other potential hazards that could account for their illness. In studies that use proxy reports, different relatives may respond differently. Garfinkel et al. (1985) provides some insight into this phenomenon by showing that if the response came from the patient, the odds ratio was 1.0, if from the husband it was 0.92, and if from the daughter or son, 3.19 (Table 4). More work is needed on the validity of ETS-exposure information obtained from different relatives before we can evaluate which of these relative risks is closer to the truth.

In general, possible reporting bias represents a serious problem in case-control studies because it can produce a systematic artefact. It is particularly worrisome in that it cannot be effectively measured.

We also need to consider misclassification that can occur in both retrospective and prospective studies. Lee has proposed (Lee et al. 1986; Lee 1987) that the reported ETS effect on lung cancer risk can be explained by a misclassification of smokers as nonsmokers. According to these studies, a substantial percentage of respondents misrepresent their smoking habits. Using a 10.0% misclassification rate of ex-smokers as self-reported neversmokers coupled with the concordance of spouses' smoking habits,

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Table 4. Data from Garfinkel et al. (1985) by type of respondent

	Husband's smoking habits at home		
	N of cases	OR	95% C.I.
Self	16	1.00	0.55– 1.74
Husband	34	0.92	0.63– 1.34
Daughter/son	48	3.19	0.91–11.19
Other	36	0.77	0.57– 1.03

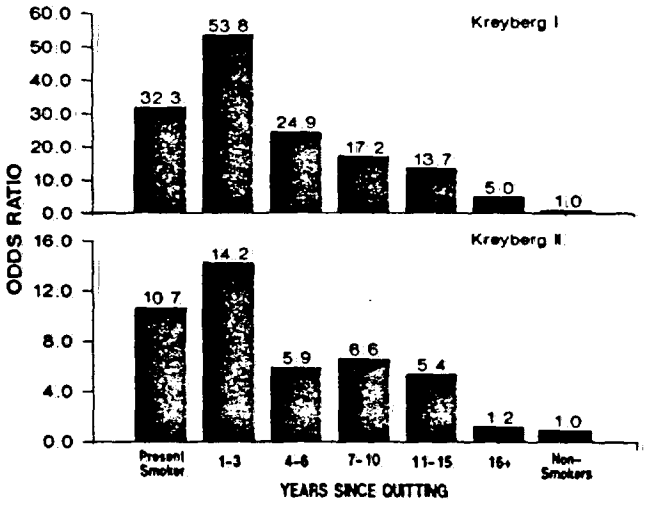

Fig. 1. Odds ratio of male ex-smokers for Kreyberg I (N = 687) and Kreyberg II (N = 301) lung cancer by years since quitting (controls = 6534). Source: American Health Foundation data

Lee calculated that an apparent increase in lung cancer risk can be obtained among nonsmokers married to smokers that approximates the increased risk observed in a number of epidemiologic studies (Lee 1987). At the extreme, Garfinkel et al. (1985) showed that 40% of lung cancer cases classified as "nonsmokers" in the hospital chart were in fact smokers as determined by interview. Although such a high rate of misclassification does not occur when cases are interviewed personally, to some extent denial is likely to occur even then, particularly among ex-smokers who had stopped smoking ten or more years ago. The risk of lung cancer among long-term ex-smokers, and even among ex-smokers who quit more than 16 years earlier, does remain elevated above the rate among those who never smoked (Fig. 1). Denial of past smoking may also not be uncommon in populations where smoking is or was socially unacceptable, as is the case among older Japanese women.

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Table 5. Percent of lung cancer cases who never smoked by histologic group (A.H.F. data)

	Males				Females			
	KI*		KII**		KI*		KII**	
	[%]	N	[%]	N	[%]	N	[%]	N
1969–1973	1.2	488	5.6	142	10.7	103	23.7	76
1974–1976	1.6	887	3.0	305	16.4	263	25.3	146
1977–1980	2.1	628	4.6	390	5.6	231	22.0	245
1981–1985	1.4	725	5.6	463	6.8	311	16.6	284

* Kreyberg I
** Kreyberg II

Another problem for epidemiologists involves subgroup analysis (Stallones 1987). Investigators are likely to examine numerous subgroups, and then prefer to present those subgroups that best fit the hypothesis. This tendency represents an inherent problem in epidemiology. The investigator should at a minimum give an idea of how many subgroups were originally examined and how many subgroups were discarded.

Temporality

One of the factors that led to the conclusion that active smoking causes lung cancer was that the increase in cigarette consumption preceded the increase in lung cancer rates, first in men and later in women. Enstrom (1979) has reported an increase in the lung cancer rate in nonsmokers over recent years, suggesting that factors in addition to personal cigarette smoking influence lung cancer mortality rates. The groups examined, however, are not strictly comparable, and misclassification of smokers as nonsmokers in the national surveys needs to be considered. Our data from a long-term, hospital-based case-control study do not indicate an increase in the percentage of male nonsmokers with lung cancer in either of the two main histologic groupings (Kreyberg I and II) over the last 30 years (Table 5).

In fact, the percentage of nonsmokers with lung cancer among women has declined, which may be a consequence of the diminishing pool of women who have never smoked.

Biological Plausibility

Several studies have demonstrated that most tumorigenic agents are present in undiluted sidestream smoke in higher concentrations than in mainstream smoke (Hoffmann et al. 1983; National Academy of Sciences 1986; Hoffmann and Wynder 1986) (Table 6). Biochemical studies indicate that nonsmokers exposed to ETS have levels of nicotine or cotinine in the blood or urine that are about 1/100th the level seen in active smokers (Table 7) (Jarvis et al. 1984; National Academy of Sciences 1986). Some of the nicotine measured in the blood and urine represents nicotine that is absorbed by the saliva of nonsmokers and does not reach the lung directly (Jarczyk et al. 1987). It is important to

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Table 6. Distribution of compounds in undiluted cigarette mainstream smoke (MS) and sidestream smoke (SS)

Nonfilter cigarettes

	MS	SS/MS
(A) Vapor phase		
Carbon monoxide	10 – 23 mg	2.5– 4.7
Carbon dioxide	20 – 40 mg	8 – 11
Benzene	20 – 50 µg	10
Formaldehyde	5 – 100 µg	0.1–≈50
Acrolein	50 – 100 µg	8 – 15
Acetone	100 – 250 µg	2 – 5
Hydrogen cyanide	400 – 500 µg	0.1– 0.25
Hydrazine	24 – 43 ng	3.0
Ammonia	50 – 170 µg	40 – 170
Methylamine	11.5 – 28.7 µg	4.2– 6.4
Nitrogen oxides	50 – 600 µg	4 – 10
N-nitrosodimethylamine	10 – 180 ng	20 – 100
N-nitrosopyrrolidine	2 – 110 ng	6 – 30
(B) Particulate phase		
Particulate matter	15 – 40 mg	1.3– 1.9
Nicotine	1 – 2.5 mg	2.6– 3.3
Phenol	60 – 140 µg	1.6– 3.0
Catechol	100 – 350 µg	0.6– 0.9
Hydroquinone	110 – 300 µg	0.7– 0.9
Aniline	360 ng	30
2-Toluidine	30 – 160 ng	19
2-Naphthylamine	4.3 – 27 ng	30
4-Aminobiphenyl	2.4 – 4.6 ng	31
Benz(a)anthracene	40 – 70 ng	2 – 4
Benzo(a)pyrene	10 – 40 ng	2.5– 3.5
N'-Nitrosonornicotine	120 –3,700 ng	0.5– 3
NNK	120 – 950 ng	1 – 4
Cadmium	100 ng	7.2
Nickel	20 –3,000 ng	13 – 30
Polonium-210	0.03– 1.0 pCi	?

note that nicotine occurs in ETS primarily as a vapor phase constituent rather than in the particulate matter of the aerosol as is the case in mainstream cigarette smoke (Eudy et al. 1987). Measurement of nicotine or its metabolites will, therefore, not reflect the proportional uptake of particulate matter from ETS. In the light of our present knowledge of dose-response in carcinogenesis and because the carcinogenic activity of tobacco smoke as measured in animal systems is relatively low, the question needs to be raised whether the carcinogenic potential of inhaled ETS suffices to induce lung cancer. Hoffmann and Hecht (1985) have proposed nicotine-derived nitrosamines in ETS as organ-specific carcinogens for the lung. It is possible that these chemicals reach the lungs in sufficient dose to induce neoplastic changes. These carcinogens may also be formed endogenously from inhaled or ingested nicotine and appropriate nitrosating agents (Hoffmann and Hecht 1985). Tumor promoters are less likely to play a role in ETS

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Table 7. Approximate relations of nicotine as a parameter between non-smokers, passive smokers and active smokers[a]. (From Jarvis et al. 1984)

Nicotine/cotinine	Non-smokers without ETS exposure No. = 46		Non-smokers with ETS exposure No. = 54		Active smokers No. = 94
	Mean value	% of active smokers value	Mean value	% of active smokers value	Mean value
Nicotine (ng/ml)					
in plasma	1.0	7	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1*	0.7	1,750
Cotinine (ng/ml)					275
in plasma	0.8	0.3	2.0*	0.7	275
in saliva	0.7	0.2	2.5**	0.8	310
in urine	1.6	0.1	7.7**	0.6	1,390

[a] Differences between non-smokers exposed to ETS compared with non-smokers without exposure
* $p < 0.01$
** $p < 0.001$

carcinogenesis than in active smoking because of their much lower concentration. In general, tumor promoters are effective only when applied repeatedly in relatively large amounts.

In considering the existing data on ETS exposure and lung cancer, it is noteworthy that Auerbach et al. (1961) showed only minor histological changes in the bronchial epithelium of nonsmokers and found that the ciliated columnar epithelium that covers their bronchi were largely intact. Deposition of carcinogenic smoke particulates can take place only upon inhibition of the protective functioning of the lung clearance system. Squamous cell lung cancer can arise only from ciliated columnar cells that have undergone squamous metaplasia.

An active smoker with each puff from a cigarette inhales a volume of 35–50 ml of a concentrated aerosol containing 3–5 billion particles per ml that adversely affect the protective cilia and mucous defense system of the bronchi (Ferin et al. 1965). The passive smoker is at no time exposed with such force to such a highly polluted inhalant. Furthermore, ETS particles are more likely to be deposited in the upper respiratory tract and not predominantly in the bronchi as is the case in active smoking. Thus, our respiratory defense system may be able to deal more readily with the relatively lighter deposition of particles and exposure to volatiles in ETS, as the observation by Auerbach et al. (1961) would suggest.

Future Studies

Future epidemiological studies on the association of ETS with lung cancer should attempt to avoid the pitfalls discussed above. The definitive evidence that a factor causes

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human cancer requires support from descriptive, metabolic, and molecular epidemiology.

Beyond extension of prospective studies, such as those now in progress by Garfinkel and Stellman at the American Cancer Society, we suggest:

1) Continuing ongoing case-control studies with special reference to histologic type and careful consideration of methodological issues.
2) Estimating the relative importance of ETS exposure in different settings – in the home, in the workplace, in social situations, and during transportation.
3) Further studying lung cancer rates among pipe and cigar smokers, and, if feasible, among nonsmokers exposed to ETS from these products.
4) Studying lung cancer incidence in groups occupationally exposed to high levels of ETS at their worksite such as waiters, bartenders, train conductors, airplane personnel, and office workers.
5) Studying bronchial epithelium in autopsy material of established never-smokers whose exposure to ETS is known.
6) Determining the incidence of lung cancer by histological type in confirmed never-smokers.
7) Comparing the presence of adducts of tobacco-specific carcinogens with DNA in smokers, passive smokers, and "never-smokers" (Hoffmann and Hecht 1985; Hecht et al. 1987).

In summary, verification of the possible association of ETS and lung cancer represents an important challenge to epidemiologists, laboratory scientists, and public health authorities. The public is entitled to inhale the cleanest possible air regardless of whether ETS is proven to be cancer-inducing. Additional efforts on the part of epidemiologists are required to firmly establish the nature and significance of the reported associations between passive smoking and lung cancer.

References

Akiba S, Kato S, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Res 46:4804–4807

Auerbach O, Stout AP, Hammond EC, et al (1961) Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. N Engl J Med 265:253–267

Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. In: Grundman E (ed) Cancer campaign, vol 6. Cancer epidemiology. Fischer, Stuttgart, pp 199–202

Correa P, Fontham E, Pickle L, Lin Y, Haenszel W (1983) Passive smoking and lung cancer. Lancet 2:595–597

Dalager NA, Pickle LW, Mason TJ, et al (1986) The relation of passive smoking to lung cancer. Cancer Res 46:4808–4811

Enstrom JE (1979) Rising lung cancer mortality among nonsmokers. J Natl Cancer Inst 62:755–760

Eudy LW, Thome FA, Heavner DL, Green CR, Ingebrethsen BJ (1985) Studies on the vapor-phase distribution of environmental nicotine by selected trapping and detection methods. Pres. 39th Tobacco Chemists Res Conf, 1985, p 25

Ferin J, Urbankova G, Vlokova A (1965) Influence of tobacco smoke on the elimination of particles from the lungs. Nature 206:515–516

Garfinkel L (1981) Time trends in lung cancer mortality among non-smokers and a note on passive smoking. J Natl Cancer Inst 66:1061–1066

2023381454

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: A case-control study. J Natl Cancer Inst 75:463–469

Greenberg RA, Haley NJ, Etzel RA, Loda FA (1984) Measuring the exposure of infants to tobacco smoke: nicotine and cotinine in urine and saliva. N Engl J Med 310:1075–1078

Hecht SS, Carmella SG, Trushim N, Foiles PG, Lin D, Rubin YM, Chung FL (1987) Investigations on the molecular dosimetry of tobacco-specific N-nitrosamines. International Agency for Research on Cancer, Lyon [IARC Sci Publ 84:423–429]

Hirayama T (1981a) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study in Japan. Br Med J 282:183–185

Hirayama T (1981b) Nonsmoking wives of smokers have a higher risk of lung cancer [Letter]. Br Med J 283:916–917

Hoffmann D, Hecht S (1985) Nicotine-derived N-nitrosamines and tobacco-related cancer: Current status and future directions. Cancer Res 45:935–944

Hoffmann D, Wynder EL (1986) Chemical constituents and bioactivity of tobacco smoke. In: Zaridze DG, Peto R (eds) Tobacco: A major international health hazard. International Agency for Research on Cancer, Lyon, IARC Sci Publ 74:145–65

Hoffmann D, Haley NJ, Brunnemann KD, Adams JD, Wynder EL (1983) Cigarette sidestream smoke: formation, analysis and model studies on the uptake by nonsmokers. US-Japan meeting "New Etiology of Lung Cancer", Honolulu, Hawaii, March 21–23, 1983

Hoffmann D, Haley NJ, Adams JD, Brunnemann KD (1984) Tobacco sidestream smoke: uptake by nonsmokers. Prev Med 13:608–613

Jarczyk L, Slerer G, Maltzan C, Luu HT, Adlkofer F (1987) Intake of nicotine from ETS via different inhalation routes. Proceedings of Third International Conference on Indoor Air Quality (in press)

Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y (1984) Biochemical markers of smoke absorption and self-reported exposure to passive smoking. J Epidemiol Comm Health 38:335–339

Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221

Koo LC, Ho JH-C, Saw D (1983) Active and passive smoking among female lung cancer patients and controls in Hong Kong. J Exp Clin Cancer Res 4:365–375

Lee PN (1987) Lung cancer and passive smoking: association an artefact due to misclassification of smoking habits? Toxicol Letts 35:157–162

Lee PN, Chamberlain J, Alderson MR (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 54:97–105

National Academy of Sciences, National Research Council (1986) Environmental tobacco smoke. Measuring exposures and assessing health effects. National Academy Press, Washington DC

Pershagen G, Hrubec Z, Svenssen C (1987) Passive smoking and lung cancer. Am J Epidemiol 125:17–24

Sandler DP, Everson RB, Wilcox AJ (1985) Passive smoking in adulthood and cancer risk. Am J Epidemiol 121:37–48

Sepkovic DW, Axelrad CM, Colosimo SG, Haley NJ (1988) Measuring tobacco smoke exposure: clinical applications and passive smoking. 80th Annual Meeting and Exhibition of the Air Pollution Control Association, New York, NY, June 21–26, 1987 (in press)

Stallones RA (1987) The use and abuse of subgroup analysis in epidemiological research. Prev Med 16:183–194

Trichopoulos D, Kalandidi A, Sparros L, MacMahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1

[USDHHS] US Dept Health and Human Services, Public Health Service, Office of Smoking and Health (1984) The health consequences of smoking: cardiovascular disease. A Report of the Surgeon General. USDHHS, US Govt. Printing Office, [DHHS Publ No (PHS) 84-50204] Washington DC

[USDHHS] US Dept Health and Human Services, Public Health Service, Centers for Disease Control (1987) The Health Consequences of Involuntary Smoking, a Report of the Surgeon General. USDHHS, US Govt. Printing Office, [DHHS (CDC) Publ No 87-8398], Washington DC

2023381455

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

[USPHS] US Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service (1964) US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control [PHS Publ No 1103] US Govt Printing Office, Washington DC

Wu AH, Henderson BE, Pike MC, Yu MC (1985) Smoking and other risk factors for lung cancer in women. J Natl Cancer Inst 74:747–751

Wynder EL (ed) (1987) Workshop on guidelines to the epidemiology of weak associations. Prev Med 16:139–212

Wynder EL, Stellman ST (1977) Comparative epidemiology of tobacco-related cancers. Cancer Res 37:4608–4622

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DISCUSSION

These calculations have shown that misclassification of smokers as non-smokers, coupled with between-spouse smoking habit concordance, may cause an *apparent* increase in risk of lung cancer among non-smokers married to smokers similar to that observed epidemiologically. Several points arise: (a) the interviews were carried out in a non-emotive, non-health context. In the cotinine study, the subjects were unaware their answers were going to be verified; (b) bias may arise because of misclassification for any reason. In this study, data-handling errors were minimised by careful processing; (c) the increased concordance for heavier smokers may explain the higher observed risk of lung cancer seen in non-smokers married to heavy smokers; (d) in this study, for women, the increase in salivary cotinine associated with spouse smoking was about 0.2% of that associated with active smoking, making a 30% increase in lung cancer risk from passive smoking very unlikely.

It is concluded that most or all of the apparently increased risk of lung cancer in self-reported non-smoking women married to smokers is attributable to bias.

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REFERENCES

1 T. Hirayama, Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan, Br. Med. J., 282 (1981), 183-185.
2 D. Trichopoulos, A. Kalandidi and L. Sparros, Lung cancer and passive smoking, Int. J. Cancer, 27 (1981) 1-4.
3 P.N. Lee, J. Chamberlain and M.R. Alderson, Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases, Br. J. Cancer, 54 (1986) 97-105.
4 C. Hugod, L.H. Hawkins and P. Astrup, Exposure of passive smokers to tobacco smoke constituents, Int. Arch. Occup. Environ. Health, 42 (1978) 21-29.
5 C. Feyerabend and M.A.H. Russell, Rapid gas-liquid chromatographic determination of cotinine in biological fluids, Analyst, 105 (1980) 998-1001.
6 M.R. Alderson, P.N. Lee and R. Wang, Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked, J. Epidemiol. Community Health, 39 (1985) 286-293.

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Toxicology Letters, 35 (1987) 163-168
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MISCLASSIFICATION OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE: ITS POTENTIAL INFLUENCE ON STUDIES OF ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER*

(Passive smoking; response bias)

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SUMMARY

The effects of selection, confounding, misclassification and bias must be eliminated from case-control studies of 'passive smoking' and lung cancer before a meaningful interpretation can be made. Misclassification includes the misclassification of the subject's non-smoking status, of the disease status or of the spouse's smoking habits. This paper shows that inflation of the amount smoked by the husbands of female lung cancer cases may have accounted for the apparent 'dose-response' relationships in 3 widely referenced case-control studies.

INTERPRETATION OF CASE-CONTROL RESULTS

Much of the literature on the association of 'passive smoking' with lung cancer consists of case-control studies of non-smoking women in which exposure to environmental tobacco smoke (ETS) from the husband's smoking is retrospectively estimated by interview of the subject or, if deceased, of a close relative or friend. Apparent 'dose-response' relationships are taken as supporting the claim that exposure to ETS increases the risk of lung cancer, i.e., a causal interpretation. This

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Abbreviations: ETS, environmental tobacco smoke.

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paper considers the contribution which differential misclassification of exposure might make to these results.

Consider the stages leading to a subject's enrolment in one of these studies. A subject must first be a patient in the selected hospital or hospitals and agree to participate in the study. She must be listed in hospital records or tumor registries as having been diagnosed with the index disease for cases or controls and must satisfy specified demographic criteria with regard to sex, age (possibly) and marital status. In addition, each potential subject must have been listed in hospital records as a non-smoker [1] or be classified as one at interview (note that 40% of women with lung cancer, classified as 'non-smokers' in hospital records, had been smokers at some time or still were, whereas only 8.5% of non-smoking controls were similarly misclassified [1]). Next, the respondent must be selected. This may be the subject herself or her next of kin. The subject's exposure to ETS, usually from her husband, is estimated by interviewing the respondent. The interview may be structured and follow a carefully designed questionnaire or be relatively unstructured.

Each of these stages presents an opportunity for selection bias and misclassification errors to occur. A case-control study of female lung cancer and exposure to ETS therefore presents ample opportunity for artifacts to generate statistically significant results. In addition, confounding may also mimic 'dose-response' effects.

Biased selection of subjects and confounding

Cases, defined as currently married lifelong non-smoking female lung cancer patients, are rare and are not typical of the population. Their 'achieved status' [2] and that of the controls may introduce selection bias into the study. In addition, husband's smoking has been shown to be confounded with age, marital status, education, alcohol and marijuana use [3]. Husbands and wives share the same life style. ETS may therefore be a 'marker' for some other factor.

Misclassification

Misclassification of the subject's diagnosis, her smoking status or of her ETS exposure may occur. Thus, Weiss [4] highlights misclassification of the subject's disease status, her ETS exposure or both as possible explanations for the results found in the epidemiological literature. Misclassification has been shown to attenuate (i.e., underestimate) the true relative risk [5]. By converting to fixed end points, Kraemer [6] has shown that this is true for all measures of association, when misclassification is randomly distributed. Such results assume, however, that the misclassification occurs at the same rate and in the same direction in cases and controls. Misclassification of smoking wives as non-smokers is known to occur [7, 8]. If the wife of a smoker gives up smoking or denies smoking and is consequently misclassified as a non-smoker rather than an ex-smoker or current smoker, her subsequent lung cancer may be associated, in fact, with her smoking rather than

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with her exposure to her husband's smoking. When hospital records are used to classify subjects, substantive misclassification is likely [9]. It has been reported [10] that, since husbands and wives tend to share smoking habits, as little as 5% misclassification among cases can produce a risk ratio of 1.42 in the absence of any effects whatever from exposure to ambient tobacco smoke.

Misclassification may also occur in classifying exposure to husband's smoking, especially if the next of kin responds for a deceased subject (more likely for lung cancer cases than for controls). The respondent is not 'blind', i.e., the respondent knows whether the subject has or had lung cancer or the 'control' disease. In this situation it is postulated that a respondent will tend to inflate the amount smoked by the husband for cases, but not for controls. This is called 'differential misclassification'. As epidemiologists have long recognised, 'when differential misclassification occurs (as in selective recall in case-control studies) the bias can be in either direction and can be great' [11].

METHODS

In the following we estimate the amount of differential misclassification required to mimic the reported results in 3 studies. It is noteworthy that in no study to date has the ETS exposure been measured directly. Rather, a coarse grouping of the amount smoked by the husband is used. This classification is derived from a respondent's answers to questions on the husband's long-term smoking habits, and is, in fact, only weakly associated with the ETS exposure of the non-smoking wife. In fact, 47% of currently non-smoking wives of smokers report less than 1 h per week ETS exposure in the home [3].

The estimation of differential misclassification rates from case-control studies requires an assumption to reduce the number of parameters. We assume that the classification of a case's 'exposure' is biased upwards and that there is no misclassification among controls. Here the husband's smoking habits are categorized so that $i = 0$ represents a non-smoker, $i = 1$ a light, occasional or ex smoker and $i = 2 \ldots m$ increasing amounts of smoking. Now let $P_i p_i$ represent the proportion of cases and controls, respectively, where the husband's smoking level is classified as $i = 0,1$ to m, so that

$$\Sigma P_i = \Sigma p_i = 1$$

Then, if N,n are the number of cases and controls in the study, respectively, a regular 'dose-response' relationship between husband's smoking classification and lung cancer will have proportions $P_i P_j p_i p_j$ such that, for all $i < j$,

$$\frac{P_i}{P_i} < \frac{P_j}{P_j}$$

Because individual cases are at risk of being misclassified, discrete steps of $1/N$ are

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taken iteratively to find the minimum misclassification rate which will reproduce the 'dose-response' relationship reported in an individual study. The misclassification rates given below are found by reducing the exposure classification one case at a time until $P_i = p_i$ for all i, to the extent possible with discrete data.

RESULTS

3 case-control studies [1, 12, 13] report statistically significant trends in non-smoking women with lung cancer as the husband's reported smoking classification increases.

Thus, Garfinkel et al. [1] give a progression of odds ratios of 1.00, 1.15, 1.08 and 2.11 for 134 cases and 402 controls reportedly exposed to 0, <10, 10-20 and >20 cigarettes/day smoked by the husband at home. Pooling the intermediate categories gives increasing odds ratios of 1.00, 1.14 and 2.11 for exposures to 0, 1-19 (where 1-19 includes pipe or cigar) and >20 cigarettes/day. Correa et al. [13] give odds ratios of 1.00, 1.18 and 3.52 for reported exposures to 0, 1-40, and >40 pack-years smoked by the husband for 22 cases and for 133 controls. Trichopoulos et al. [12] give odds ratios of 1.00, 1.76 and 2.65 for the 3 exposure categories (non-, former and current smoker) in 40 cases and 149 controls.

Given the assumptions discussed above, Garfinkel's results can arise if 17 of the husbands of his 134 cases are misclassified upwards, a case misclassification rate of 13%. Correa's results can arise if 9 of his 22 cases' husbands are misclassified, a case misclassification rate of 41%. For Trichopoulos, the reported trend could have arisen from a case misclassification rate of 40%, i.e., if 16 of 40 cases' husbands were misclassified upwards. Because of the relatively larger number of cases in the first study [1], the overall case misclassification rate in the three studies required to reproduce the quoted results is 21%.

Although misclassification of exposure among cases has a disproportionate effect on the findings of these studies, another approach is to assume that the rates of misclassification are equal in cases and controls but in different directions. With this assumption, Garfinkel's results [1] can arise from a subject differential misclassification rate of 7%. Likewise, Correa's findings [13] may have arisen from a subject differential misclassification rate of 19%. A 20% overall differential misclassification rate will account for the trends reported by Trichopoulos in Tables 2 and 3 of his paper [12].

DISCUSSION

The findings of 3 case-control studies of lung cancer which show significant trends with 'exposure' to ETS can be generated by postulating differential misclassification of case exposure in the range of 13-40%. The significance of this finding rests on the validity of the underlying assumptions used in deriving these

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rates of case or subject misclassification.

That misclassification exists in these studies is now widely accepted [3, 4, 9, 14-17]. In general, respondents are more likely to falsely inflate exposure if the case died of cancer than of some other disease [18].

More particularly, there is indirect evidence for the presence and effect of differential misclassification of exposure to ETS. For example, Garfinkel et al. [1] show that the effect of ETS exposure at home is null (an odds ratio of 1) when the case or her husband is the respondent; however, this null result is converted into an odds ratio of 3 when the son or daughter is the respondent.

Again, Table 3 of [15] suggests that differential misclassification may exist. This shows that 4 of 16 spouses of lung cancer cases (25%) contradicted the case by describing themselves as smokers whereas only 1 in 41 (2%) spouses of matched controls contradicted the control by describing themselves as smokers. Here there are two possible explanations. Either the case has denied her husband's smoking, or the husband has exaggerated his own smoking. In practice there is likely to be some behavior of each type. We assume however that this situation is indicative of inflation of the amount smoked by the husband when the case is the respondent.

The most recent case-control study of ETS and lung cancer [15], one which went to some pains to verify exposure classification, provided evidence suggesting a case misclassification rate of exposure as high as 25%. This figure may be compared to the 21% overall case misclassification rate required to produce the results in the 3 studies under review. Both figures may in turn be compared with a misclassification rate of 15% which Letzel and Johnson [19] found was required to invalidate a case-control study of ETS.

In summary, when a spouse's smoking status is used to estimate a non-smoker's ETS exposure, ' a considerable amount of misclassification' [3] may result. Since selection bias and confounding must also be considered, extreme caution is required in the interpretation of these studies. This is especially so when the literature as a whole contains several studies reporting no significant association between ETS exposure and lung cancer [15, 16, 20], as well as various inconsistencies, both among and within studies.

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REFERENCES

1 L. Garfinkel, O. Auerbach and L. Joubert, Involuntary smoking and lung cancer: a case-control study, JNCI 75 (1985) 463-469.

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2 S. Graham and R. Graham-Tomas, Achieved status as a risk factor in epidemiology, Am. J. Epidemiol. 122 (1985) 553-558.
3 G.D. Friedman, D.B. Petitti and R.D. Bawol, Prevalence and correlates of passive smoking, Am. J. Publ. Health, 73 (1983) 401-405.
4 S.T. Weiss, Passive smoking and lung cancer. What is the risk? Am. Rev. Resp. Dis. 133 (1986) 1-3.
5 B. Gladen and W.J. Rogan, Misclassification and the design of environmental studies, Am. J. Epidemiol. 109 (1979) 607-616.
6 H.C. Kraemer, The robustness of common measures of 2 × 2 association to bias due to misclassifications, Am. Stat. 39 (1985) 286-290.
7 M.R. Alderson, P.N. Lee and R. Wang, Risk of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked, passive smoking and other factors, Report vol. 1 Text p. 94 (1986).
8 C. Vutuc, Quantitative aspects of passive smoking and lung cancer, Prev. Med. (1984) 13, 698-704.
9 H. Gellband, B. Larson and K. Kronesbusch, Passive smoking in the workplace: selected issues. Office of Technology Assessment Staff Paper (1986) May.
10 P. Lee, p.733 of G. Lehnert, Roundtable Discussion, Prev. Med., 13 (1984) 730-746.
11 K.T. Copeland, H. Sheckoway, A.J. McMichael and R. Holbrook, Bias due to misclassification in the estimation of relative risk, Am. J. Epidemiol., 105 (1977) 488-495.
12 D. Trichopoulos, A. Kalandidi, L. Sparros and B. MacMahon, Lung cancer and passive smoking, Int. J. Cancer, 27 (1981) 1-4.
13 P. Correa, L.W. Pickle, E. Forham, Y. Lin and Haenszel, Passive smoking and lung cancer, Lancet, 2 (1983) 595-597.
14 H. Özkaynak, Bias due to misclassification of personal exposures in epidemiologic studies of indoor and outdoor air pollution. Proc. Int. Conf. Indoor Air Quality and Climate, 2 (1984) 377-384.
15 P.N. Lee, J. Chamberlain and M.R. Alderson, Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases, Br. J. Cancer, 54 (1986) 97-105.
16 G.C. Kabat and E.L. Wynder, Patterns of exposure to environmental tobacco smoke in a group of hospitalized patients, Proc. Air Pollution Control Assoc. 79th. Annu. Meet., Minneapolis, June 22-27, 1986.
17 N. Wald, Personal communication.
18 E.R. Greenberg, B. Rosner, C.H. Hennekens, R. Rinsky and T. Colton, An investigation of bias in a study of nuclear shipyard workers, Am. J. Epidemiol. 121 (1985) 301-308.
19 H.W. Letzel and L. Clark Johnson, The extent of passive smoking in the Federal Republic of Germany, Prev. Med., 13 (1984) 717-729.
20 L.C. Koo, J.H. Ho and D. Saw, Is passive smoking an added risk factor for lung cancer in Chinese women? J. Exp. Clin. Cancer Res. 3 (1984) 277-283.

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Lung cancer and passive smoking

SIR,—Your article by Professor Nicholas Wald and others (8 November, p 1217) on passive smoking and lung cancer contained a statistical analysis which was essentially repeated in a report of a committee of the National Research Council of the United States. Professor Wald was a member of that committee and apparently was the principal architect of the epidemiological aspects of that work.[1]

A contemporaneous survey of epidemiological studies on passive smoking and lung cancer was given in an editorial by Blot and Fraumeni in the *Journal of the National Cancer Institute*.[2] The published reports covered by Professor Wald and colleagues and by Blot and Fraumeni largely overlapped. Substantially similar estimates of relative risk were arrived at, 1·34 or 1·35, and in both cases were nominally significant.

Similar concerns about bias were expressed, specifically that women reporting themselves as non-smokers might actually be active smokers or ex-smokers and that non-smoking women not exposed to smoking at home might still have some exposure away from home. Other possibly more serious biases in the studies conducted were not considered. (These include publishing bias: if an investigator got a weakly or insignificantly negative result for the role of passive smoking in lung cancer would he bother submitting it for publication? And if he did, would it be accepted? There seems to be a tendency towards accepting uncritically or less critically manuscripts which are on the right side of the fence on the issue of passive smoking.)

Consideration of the first of these two biases led to a reduction in the estimated relative risk from 1·35 to 1·30 for the paper of Professor Wald and his colleagues but from 1·34 to 1·15 in the National Research Council report. This source of bias cannot fully account for the excess over unity of the relative risk, albeit the National Research Council report suggests that statistical significance would no longer obtain. And the possibility of other biases is noted.

The two survey studies make differing adjustments for exposure to passive smoking away from home. While Professor Wald and his colleagues make an upward adjustment of 18%, from a relative risk of 1·30 to 1·53, the National Research Council report makes an upward adjustment of only 8%, from 1·15 to 1·24.

For assessing statistical significance, this last adjustment is not relevant. It presupposes that passive smoking does increase risk, for if it did not the adjustment would not be needed. But relevance would attach if one wished to estimate the toll in lung cancer attributable to passive smoking.

The National Research Council report notes a study by Jarvis *et al* on biochemical markers of smoke absorption.[3] From that work one would have to judge that the claim of being a non-smoker was more frequently false than has been allowed for in the bias adjustments that have been made. Also, the data on cotinine concentrations in the plasma, saliva, and urine reported by Jarvis *et al* suggest that the relative risk associated with passive smoking would be quite limited, say of the order of 1·05. Passive smokers had, on average, cotinine values 0·5% of the way between the level for those not exposed to passive smoking and the level for active smokers. Assuming active smoking to have a relative risk of 10, added risk of 900%, the predicted relative risk for passive smoking would be 1·045.

It is interesting that the National Research Council report shows a predicted relative risk of 1·14 based on dosimetric considerations. The underlying assumption was that passive smoking had only 1% of the effect of active smoking. That 1% effect was then coupled with a relative risk of 15, added risk of 1400%, for active smoking.

In the event, whether the true relative risk is 1·05 or 1·14, it is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith according to one's choice.

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1 National Research Council Committee on Passive Smoking, Board on Environmental Studies and Toxicology. *Environmental tobacco smoke: measuring exposures and assessing health effects*. Washington, DC: National Academy Press, 1986.
2 Blot JB, Fraumeni JF Jr. Guest editorial. Passive smoking and lung cancer. *Journal of the National Cancer Institute* 1986;77: 993-1000.
3 Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vessey C, Salloojee Y. Biochemical markers of smoke absorption and self reported exposure to passive smoking. *J Epidemiol Community Health* 1984;38:335-9.

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In conclusion, therefore, the reference bias shown in this study seems to be real. Such a finding has important implications, since there is no reason to believe that rheumatologists are more biased than others in selecting references. A reader tracing the literature on any new drug using the reference lists given in the articles might risk obtaining a biased sample. Reference bias has another serious implication: it may render the conclusion of the individual article less reliable. Is this also true for review articles, and for other disciplines in medicine?

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References

1 Poynard T, Conn HO. The retrieval of randomized clinical trials in liver disease from the medical literature: a comparison of MEDLARS and manual methods. *Controlled Clin Trials* 1985;6: 271-9.
2 Dickersin K, Hewitt P, Mutch L, Chalmers I, Chalmers TC. Perusing the literature: comparison of MEDLINE searching with a perinatal trials database. *Controlled Clin Trials* 1985;6: 306-17.
3 Sackett DL. Bias in analytic research. *J Chronic Dis* 1979;32:51-63.
4 National Library of Medicine. *Medical subject headings: annotated alphabetic list*. Bethesda, Maryland: NLM, 1985.
5 Institute for Scientific Information. *Science citation index: Journal citation reports*. Philadelphia: ISI; 1986.
6 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chronic Dis* 1967;20:637-48.

Towards a reduction in publication bias

ROBERT G NEWCOMBE

Abstract

Current practice results in the publication of many research studies in medical and related disciplines which may be criticised on the grounds of inadequate sample size and statistical power. Small studies continue to be carried out with little more than a blind hope of showing the desired effect. Nevertheless, papers based on such work are submitted for publication, especially if the results turn out to be statistically significant. There is confusion about what makes a result suitable for publication. Often there is a preference for statistically significant results at the peer review stage. Consequently published reports of small studies tend to contain too many false positive results and to exaggerate the true effects.

The use of a criterion of a posteriori power does not eliminate the bias; a priori power is the criterion of choice. This could be implemented by peer review of study protocols at the planning stage by funding bodies and journals.

Introduction

Profound biological and behavioural differences between human beings mean that statistical methods have to be used in presenting medical research findings in an unbiased way. Hence statisticians have devised methods of estimation and significance testing, which are now widely used. Nevertheless, though the mathematical aspects of these methods are acceptable, what is done with the results commonly leads to serious selection bias. An article that reports a statistically significant difference between two treatments is more likely to be published than one which does not. Many research studies have inadequate numbers of subjects, and significance can be attained only if chance conveniently exaggerates the difference.

So long as statistical significance is used as a major criterion of acceptability for publication the published results of medical research will contain a high proportion of false positive results. Thus quantitative estimates of treatment effects taken from published work cannot be regarded as free from bias. There are established methods to calculate the power of a study, which is the probability of detecting a specified, important difference using a test with a set significance level. The interpretation of statistical power is satisfactory only when it is calculated with values specified at the design stage of the study. The proper method to assess the adequacy of the sample size is by peer review of values specified in the protocol. If this is done the significance level eventually attained is no longer relevant to selection for publication.

Importance of sample size

Manuscripts submitted to medical journals often contain serious statistical faults.[1] Various steps have been taken to remedy this,

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notably the checklists used by the *BMJ*,[3] and there is now also an increased awareness of the need for therapeutic efficacy to be evaluated with randomised controlled trials. Nevertheless, power calculations are still rarely used.[4]

Conventional significance testing (table I) leads to great emphasis on the type I error rate α, but the type II error rate β and its complement, the power $1-\beta$, though very important, are neglected.[5] In particular, in a clinical trial the number of subjects required depends on the α and β levels chosen, the treatment difference of interest, and the degree to which the treatment effect varies between subjects. The choice of the first three of these is somewhat arbitrary, and the fourth may be difficult to estimate. Nevertheless, the study is likely to be valid only if values are chosen for these parameters and the resulting sample size requirement determined, whether by the use of formulas,[6] diagrams,[5] or tables.[6]

TABLE I—*The significance testing paradigm. α and β denote the frequencies with which type I errors and type II errors are made. $1-\beta$ is known as the power of the test*

	Decision from significance test	
True state of nature	Accept H_0	Reject H_0
H_0 valid	True negative $1-\alpha$	False positive α
H_0 not valid	False negative β	True positive $1-\beta$

The most obvious consequence of an inadequate sample size is that investigators may well not show a clinically important effect. Such a false negative result, if propagated by publication, is apt to be widely misinterpreted as a demonstration that there is no difference between the treatments. This has provoked two responses among those who decide what is to be published. Firstly, statisticians advocate a shift of emphasis away from significance testing and towards estimation and confidence intervals.[7] A wide confidence interval is understood as implying that large, potentially important differences cannot be ruled out. The confidence interval approach may also help in a wider context—for instance, in showing that the results of two apparently disparate studies are not incompatible, the truth perhaps being somewhere between their two estimates.

The second response is to exclude small studies, with high β, from publication. There are three approaches in which this may be done. Firstly, attainment of a desired level of significance may be used as a criterion. This seems plausible because, for a fixed α, both the attained significance level p and the type II error rate β reflect the sample size. Nevertheless, p (unlike α) depends on sampling variation and the use of this criterion leads to publication bias. Secondly, assessment based on statistical power calculated from the data gives the appearance of greater soundness; it does not fall into the obvious trap of the first approach and is based on data rather than on the uncertainty of a prior targeted difference. In reality, however, the requirement of significance using an α level of 0·05 and an a posteriori β of 0·2 amounts to nothing more than statistical significance at a more stringent level of $\alpha=0{\cdot}005$ and thus also does not avoid publication bias. This kind of β value is akin to p, not to α, and includes sampling variation. The third approach is to impose the requirement of an adequately low β value assessed a priori; this does not lead to bias since the β value is not subject to sampling variation.

Thus results based on studies which had a poor prospect of yielding useful information may justifiably be rejected, but only if the criterion is based on power assessed a priori.

Nature and consequences of publication bias

Publication bias may be defined simply: significant results are preferred for publication. Attention was drawn to it as early as 1963[8] and it has been "rediscovered" several times since. Suppose the α rate chosen is 0·05. Then, just 5% of studies in which H_0 is valid will yield a test statistic significant at the 5% level. If attention is limited to studies that attain publication, however, the proportion of such false positive results is higher. The significance testing paradigm does not permit us to say what proportion of statistically significant results are false positives, but the effect of publication bias is to make this proportion disquietingly larger than it would otherwise be.

Correspondingly, studies selected for publication tend to contain exaggerated estimates of the main effects, and trials with truly modest treatment effects will achieve statistical significance only if random variation conveniently exaggerates these effects.[9] Conversely, variation is underestimated. These biases operate more strongly the more inadequate the sample size. A study with low power, where the true treatment effect is zero or small, must grossly exaggerate it (by chance) to show significance and attain a prospect of publication. False positives and exaggerated estimates may well dominate much of medical publication. This phenomenon is likely to contribute to the disparity commonly found in the results of different studies, which leads to controversy instead of well established, consistent findings. The desire to minimise the impact of false positive assertions may result in a preference for publishing findings which refute a previous claim, rather than confirmatory results—a further source of bias.

Such selection bias may equally be introduced by the editorial team (editorial selection bias) or by the researcher or supervisor or head of department (submission selection bias). At each stage a significant result may be construed as particularly encouraging and failure to attain significance as correspondingly discouraging. This operates in addition to any biases introduced because of prejudice.[10]

Publication bias continues to arise only because two conditions hold: the criteria for selecting studies for publication are inadequate, and many studies performed and submitted for publication have been done on small numbers of subjects. Significance testing, the time honoured framework for inductive inference, is evidently deficient as a selection criterion. Nevertheless, the confidence interval approach incurs the same danger of publication bias: studies in which the confidence interval for the size of the effect excludes zero are likely to be preferred for publication—a condition that is equivalent to statistical significance. It has been asserted that overconcentration on simplistic significance testing is responsible for most of the ill based criticisms of small trials.[11] The more careful approach using confidence intervals overcomes many of the difficulties. But so long as confusion remains as to what constitutes a result warranting publication a bias will ensue from submission and editorial selection processes.

The other prerequisite for publication bias is the widespread use of inadequate sample sizes. The other consequence of this is that a doctor seeking information to guide a clinical decision is confronted with a bewildering variety of conflicting claims. To remedy this dilemma "meta-analyses" or "overviews" have been constructed, which fit together results of several studies and seek to make the best use of data from studies which would otherwise yield little information. Nevertheless, published studies are still a biased sample of all the relevant work that has been done. The only prospect of eliminating this bias is to contact all investigators who may have done relevant work and ask for their unpublished data. Iain Chalmers and Thomas Chalmers are pursuing this goal in connection with the Oxford Database of Perinatal Trials, and their work should provide some evidence on the quantity of "negative" studies that either never get written up or never get published.

The high prevalence of small studies stems from the way that research is organised. Much material submitted for publication has come from studies that are regarded as the work of an individual researcher, performed within severe constraints of time and resources; often there is little more than a blind hope that the desired effect will be shown. Research output remains a major criterion for assessing candidates for promotion and so on, even though it is widely recognised to be deficient. When research output is equated with publication, however, the consequences for the standards of published work are grave. The constraints an individual investigator faces often preclude obtaining results of

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external validity, but publication in a highly regarded, widely circulated journal implies such validity, however mistaken this is given the background of inadequate statistical power.

Thus the researcher faces a dilemma: on the one hand, most studies he can perform will need the collaboration of others to attain adequate statistical power; on the other hand, any collaborative study (even if it is feasible) will deprive him of personal kudos. Only those who are remote from the researcher's dilemma—journal editors and referees, funding bodies, and (to a lesser degree) ethical committees —can uphold the highest scientific standards with no conflict of loyalties. These agents are not obliged to accept the status quo and can refuse to support or publish inadequate research. I regard it as their prerogative, if not obligation, to do so.

A radical proposal

Selection of work for funding or publication, then, should primarily be based on reasonableness a priori: Has the design adopted (explicitly or implicitly) a good prospect of yielding useful information? "Design" here includes the study idea, scientific basis, clinical relevance, originality, and so on, as well as the study's structure and the number of subjects. If all this is satisfied then the paper should be published irrespective of whether statistical significance or the targeted size of difference was attained. The difference actually observed is irrelevant to the decision (see Mahoney,[10] p 163). The assessment of scientific validity would therefore be the same, whether carried out before the study or after it. The only additional requirement a posteriori is adequate adherence to the protocol—in particular, attainment of the planned sample size.

The consequences of this shift in emphasis to a priori criteria are most important in the case of studies of inadequate power. Table II contrasts what would happen to the results of these studies under the proposed rule with what is likely to happen at present. The publication of "positive" findings would be inhibited. The advantage would be the exclusion of false positives from inadequate studies, with their grossly exaggerated estimates of differences. Against this must be weighed the cost of failing to publish true positives—which would occur quite often ($1-\beta=0{\cdot}5$), but which are based on inadequate evidence and also overestimate the difference.

Application of this principle to studies with adequate power would lead to more widespread publication of negative results (table III). True negative results would be salvaged from studies of acceptable power—though these might currently be accepted anyway, especially if supplemented with confidence intervals. This

TABLE II—*Consequences of a shift to assessment by a priori power. The case of a study with inadequate power: $1-\beta=0{\cdot}5$, $\alpha=0{\cdot}05$*

	Decision from significance test	
	Accept H_0	Reject H_0
Whether published under:		
Present practice	?No	Yes
Proposed policy	No	No

would be at the cost of publishing studies with false negative results, though these would not be too frequent ($\beta=0{\cdot}1$).

Both journal editors and funding bodies can and should require specification of statistical power. They should require that a protocol or a write up should describe clearly the details of the design of the study—in particular, the following:

(*a*) the structure;

(*b*) the choice of the most appropriate criterion variable on which to base the power calculation and the most appropriate groups to be compared;

(*c*) the size of the effect to be reliably detected and (except in the case of a binary variable) how much this effect varies between subjects;

(*d*) the sample size (specifying accrual rate and period) aimed at, with specific allowance for expected dropouts;

(*e*) consequent statistical power and the method by which it was derived.

These parameters should be identical in the protocol and in the eventual study report. The same criterion should be used to assess validity at both stages—in particular, the write up should be assessed on the basis of the values laid down before any data were collected. The only additional requirements at the publication stage would be the completion of the study as laid down in the protocol, with full information on as many subjects as were contracted for; variability in response between subjects not grossly in excess of that planned for; and the usual standards of adequate analysis, inference, and discussion.

TABLE III—*Consequences of a shift to assessment by a priori power. The case of a study with adequate power: $1-\beta=0{\cdot}9$, $\alpha=0{\cdot}05$*

	Decision from significance test	
	Accept H_0	Reject H_0
Whether published under:		
Present practice	?No	Yes
Proposed policy	Yes	Yes

This approach entails assessment of the parameters assumed on an a priori basis; they are to be judged in the light of knowledge current at the time the study was designed. Other results coming to light during the study should not be allowed to affect the judgment of validity (though occasionally a major advance occurring during this period may render the results no longer relevant).

Journal editors as well as grant awarding bodies could implement this proposal most effectively by requiring submission of protocols for peer review at the planning stage. In either case an independent review body could be used. Specialists in the subject could assess the reasonableness of the values supplied for the parameters on which the power calculation is based (particularly the smallest clinically important difference), and the verification of the power calculation would not be a formidable task for a statistician or other assessor familiar with this. These assessments, once performed for the protocol, would not need to be repeated for the write up. Consequently, having accepted a protocol as adequate and relevant, a journal could offer eventual publication, conditional only on completion of the study in adequate conformity to the protocol together with the usual requirements of adequate analysis, inference, and discussion. It would become normal practice to accept an article only if this had been done.

The work of Mahoney suggests that reviewers may find it difficult to comment on incomplete manuscripts.[10] Nevertheless, Mahoney's study is not an ideal model for the process I advocate, for two reasons. Firstly, his reason for the incompleteness of the manuscript was inadequate. It would be understood, however, that the material to be evaluated was only a protocol, even though it would be virtually unaltered in the eventual article—and this would become an accepted element of peer review (as it is, to a limited extent, with funding bodies). Secondly, Mahoney studied psychologists known to have entrenched, diametrically opposite beliefs, to a degree (I hope) not encountered often among doctors; knowing that results would shortly be disclosed, they would be reluctant to commit themselves unequivocally to a favourable stance, lest the results turned out to contradict their chosen position. At the stage of review of a protocol this possibility is more remote.

To put these recommendations into practice would be more feasible for formal, well structured study designs, such as the clinical trial, than for less formal explanatory work—for which the rationale of significance testing is more contentious. Like other alterations in editorial policy, this would best be introduced as a decisive change, as from a given date, with advance indication given, as a piecemeal approach to change is unlikely to work.[11] I

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hope that enlightened editors will take up the challenge; the lead must come from an established, prestigious journal that can afford to be choosy.

Conclusion

Publication bias is endemic and will remain so as long as the sample sizes commonly used in research are too small and the methods used to assess adequacy of sample size are deficient. Assessment by a priori criteria—in particular, systematic peer review at the planning stage—would result in a much tighter measure of control over the quality of published work, with the prospect of improvement in study design in general and statistical power in particular.

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References

1 Schor S, Karten I. Statistical evaluation of medical journal manuscripts. *JAMA* 1966;195:1123-8.
2 Gardner MJ, Machin D, Campbell MJ. Use of check lists in assessing the statistical content of medical studies. *Br Med J* 1986;292:810-2.
3 Freiman JA, Chalmers TC, Smith H, *et al*. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978;299:690-4.
4 Armitage P. *Statistical methods in medical research*. Oxford: Blackwell, 1971:186.
5 Altman DG. Statistics and ethics in medical research. III. How large a sample? *Br Med J* 1980;281:1336-8.
6 Cochran WG, Cox GM. *Experimental designs*. 2nd ed. New York: Wiley, 1957:24-5.
7 Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br Med J* 1986;292:746-50.
8 Melton AW. Editorial. *J Exp Psychology* 1962;64:553-7.
9 Pocock SJ. Current issues in the design and interpretation of clinical trials. *Br Med J* 1985;290:39-42.
10 Mahoney MJ. Publication prejudices: an experimental study of confirmatory bias in the peer review system. *Cognitive Therapy and Research* 1977;1:161-75.
11 Powell-Tuck J, MacRae KD, Healy MJR, Lennard-Jones JE, Parkins RA. A defence of the small clinical trial: evaluation of three gastroenterological studies. *Br Med J* 1986;292:599-602.
12 Lock S. *A difficult balance—editorial peer review in medicine*. London: Nuffield Provincial Hospitals Trust, 1985.

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Medicine and the Media

AT THE ANNUAL scientific meeting of the British Paediatric Association last year the prize for the best paper presented by a young paediatrician went to a member of a research group from Oxford. Papers offered for the annual meeting are examined by the association's academic board not only for their scientific worth but also for adherence to ethical standards. This paper, later published in the *Lancet*,[1] has now been condemned by certain sections of the press and by a group of members of parliament. What was the work so condemned?

Preterm infants of low birth weight live at considerable risk, particularly of cardiorespiratory failure, and the risk is increased if they have to undergo an operation. Clinical experience suggested that deep anaesthesia and narcotic analgesics would increase the risk. That and the belief that such infants have a poor perception of pain because of lack of myelinisation in the central nervous system led to the conventional practice of anaesthesia with nitrous oxide and muscle relaxants combined with artificial ventilation. In a study of 40 published reports the Oxford team found that three quarters of newborn babies undergoing surgical ligation of patent ductus arteriosus had received muscle relaxants alone or with nitrous oxide.

In the preterm infant with a poor or absent ability to cry it is difficult to tell clinically whether pain and stress are being experienced, but newer biochemical methods that detect hormones and intermediary metabolites associated with stress now make the assessment of stress more possible and prompted a re-examination of the problem by the Oxford team. The team wanted to find out whether adding a little narcotic analgesic to the accepted anaesthetic regimen might prove beneficial rather than harmful. Using these metabolic methods, they therefore compared the response to surgical ligation of patent ductus arteriosus carried out under the conventional regimen with and without the narcotic analgesic fentanyl. The possibility that fentanyl might adversely affect respiration and circulation postoperatively was also studied.

A randomised trial was designed with help from the National Perinatal Epidemiology Unit in Oxford to ensure that the results were statistically valid and that a meaningful result would be recognised as soon as possible. After only eight babies in each group had been operated on the results showed that the new regimen was significantly superior to the old not only in reducing the stress response estimated biochemically but also in improving the postoperative state. Thus for the first time good scientific evidence was produced of the need to provide deeper anaesthesia during operations on these tiny infants.

This research was commended by the distinguished American paediatrician Dr William Silverman, author of the widely acclaimed book *Human Experimentation: A Guided Step Into the Unknown*.[2] He wrote that the Oxford workers "deserve a loud vote of thanks for the ethically sound effort to subject to a rigorous test opinion based on long standing practice. And their call for further study should not fall on deaf ears. It is indeed urgent to determine the pathophysiological consequences of unrelieved pain and suffering inflicted during everyday care of newborn babies."

Members of the British Paediatric Association were thus amazed and the doctors who had done the work bewildered and distressed when after a distorted report in the *Daily Mail* entitled, "Pain-killer shock in babies' operations" (8 July) this work became the subject of a condemnatory "press release: for immediate publication" issued by some members of parliament forming the All Party Parliamentary Pro-Life Group. The *Lancet* article appeared in January, the story in the *Daily Mail* in July, and the press release from the members of parliament in August. The press release was entitled "Inhumane baby operations slammed" and the first paragraph stated:

"Fourteen members of parliament have demanded an inquiry into trials in which sixteen premature babies were given open heart surgery, eight of them without the use of pain killers to test whether or not the babies could experience pain."

The press release then said that the General Medical Council was being asked to investigate these trials with a view to bringing those responsible before its disciplinary committee. It continued:

"In a statement Sir Bernard Braine said:

'The trials seemed to us to be even more barbarous when one considers that the babies being tested for pain were given curare, a paralysing drug, so that they would have been unable to kick or struggle even if they were in agony, the obvious intention being to keep them immobile at all costs throughout the operation. Apart from this they were given only nitrous oxide (laughing gas).'"

Implying misleadingly that wisdom acquired from the research existed before it was carried out the statement went on:

"Not surprisingly post-operatively they fared far worse than the eight babies who were given pain killers. Two of the disadvantaged babies suffered from hypotension, two showed poor peripheral circulation—both of which can be indications of shock which most

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QUESTIONNAIRE ASSESSMENT OF LIFETIME AND RECENT EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

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Coultas, D. B. (New Mexico Tumor Registry, Cancer Center, U. of New Mexico Medical Center, Albuquerque, NM 87131), G. T. Peake, and J. M. Samet. Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. *Am J Epidemiol* 1989;130:338–47.

In a sample of 149 adult nonsmokers recruited in New Mexico in 1986, the authors assessed the reliability of questionnaire responses on lifetime exposure to tobacco smoke in the home. They also compared urinary cotinine levels with questionnaire reports of environmental tobacco smoke exposure during the previous 24 hours. The agreement of responses obtained on two occasions within six months was high for parental smoking during childhood: 94% for the mother and 93% for the father. For the amounts smoked by the mother and the father during the subject's childhood, the agreement between the two interviews was moderate: 52% and 39%, respectively. For the number of hours per day that each parent smoked in the home during the subject's childhood, the Spearman correlation coefficients also indicated only moderate reliability ($r = 0.18$ for maternal smoking and $r = 0.54$ for paternal smoking). For each set of interviews, responses concerning recent tobacco smoke exposure and urinary cotinine levels were correlated to only a modest degree. The authors conclude that adults can reliably report whether household members smoked during their childhood, but information on quantitative aspects of smoking is reported less reliably.

pyrrolidinones; questionnaires; tobacco smoke pollution

The term "passive smoking" refers to the involuntary exposure of nonsmokers to the combination of tobacco combustion products released by the burning cigarette and smoke components exhaled by the active smoker (1, 2). The adverse health effects of passive smoking on children and adults have been described in numerous epidemiologic investigations (1, 2). However, despite the evidence linking malignant and nonmalignant diseases with active and passive smoking, tobacco smoking remains highly prevalent worldwide (1). In the United States at present, about 30 per cent of adults are active cigarette smokers (3), so that a large proportion of nonsmokers

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in this country are involuntarily exposed to environmental tobacco smoke (1, 2).

Although some health effects of passive smoking have been convincingly demonstrated, many questions on the health effects of passive smoking remain unanswered. More precise description of exposure-response relations is needed for assessment of the adverse effects on children and the development of lung cancer. Additionally, further studies on exposure to environmental tobacco smoke in the workplace are warranted because of the high prevalence of smoking among adults and public concern about this source of exposure. In most epidemiologic studies on involuntary smoking published to date, exposure has been assessed with questionnaires; for the purposes of some investigations, the questionnaires have spanned the entire lifespans of the subjects. Questionnaires will remain the most feasible method for assessing exposure to environmental tobacco smoke in new studies. However, the reliability and validity of questionnaire measures of involuntary smoking have not been adequately characterized.

In this study, we have assessed the reliability of a comprehensive questionnaire on lifetime exposure to environmental tobacco smoke in 149 adult nonsmokers. While validity is also of interest, no appropriate standard for comparison is available for a lifetime history. Questionnaire responses with poor reliability are also likely to have poor validity. In this sample, we also examined the relation between reports of recent exposure to environmental tobacco smoke and urinary cotinine levels.

MATERIALS AND METHODS

Sample selection

Between February and December of 1986, nonsmokers aged 18 years and older were recruited from Albuquerque, New Mexico, and the surrounding communities. Recruitment was accomplished by two methods: advertisements and direct contact with subjects from a population survey (4). In both approaches, we asked for volunteers to participate in a study of indoor air quality that involved completing a questionnaire on two occasions and providing saliva and urine samples. The subjects were not informed that the study was directed specifically at exposure to environmental tobacco smoke. We attempted to stratify the sample uniformly by age and by sex but were not completely successful (table 1). Of our sample, 62 per cent were female, and only five males were aged 60 years and older.

Data collection

A structured questionnaire on lifetime and recent exposure to environmental tobacco smoke was administered by a trained interviewer to each subject on two occasions separated by approximately four to six months. Training involved familiarization and practice with the questionnaire and review of probing techniques, which were standardized. The interviews were conducted by four interviewers who completed 89.2, 5.4, 2.7, and 2.7 per cent of the first interviews and 38.2, 6.7, 54.4, and 0.7 per cent of the second interviews, respectively. We asked whether the subject's mother had smoked while pregnant with the subject, and we determined the smoking status of parents, spouses, and others from questions on whether these persons had smoked in the subject's home on a daily basis for six months or more. These questions referred to two time periods: birth to age 18 years and age 19 years to the time of the interview. These time periods were chosen to correspond to the usual ages for

TABLE 1

Age and sex distribution of 149 participants in a study of involuntary exposure to tobacco smoke, New Mexico, 1986

Age (years)	Males		Females	
	No.	%	No.	%
20–29	12	21.4	17	18.3
30–39	20	35.7	27	29.0
40–49	9	16.1	15	16.1
50–59	10	17.9	15	16.1
≥60	5	8.9	19	20.4

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living in the parents' home and subsequently living outside the parents' home. In addition, for each smoker, we asked about the type(s) of tobacco smoked (cigarette, pipe, or cigar), the amount of each type smoked in the home, the number of years each type was smoked, and the number of hours of exposure per day to each type in the home. Another set of questions asked about the amount of exposure during the previous 24 hours. The questions covered the number of smokers to which the subject was exposed, the type(s) of tobacco smoked (cigarette, pipe, or cigar), and the number of hours of exposure. These questions were asked separately for exposures at home, at work, in vehicles, and at social gatherings. At the time of the interview, a urine specimen was collected and frozen at −20 C until the cotinine assays were performed.

Cotinine assay

Cotinine was quantitated by a double antibody radioimmunoassay as described by Langone et al. (5). A specific antiserum produced in rabbits was supplied by Dr. Helen Van Vunakis of Brandeis University (Waltham, MA). Urine samples were diluted 1:4 for the assay. The sensitivity of the assay in our hands was 36 pg/tube or 0.78 ng/ml of urine (4,204 pmol/liter). Urinary creatinine concentrations were determined by the Jaffe reaction (6), and the cotinine concentrations were standardized to the creatinine concentrations. Assays were performed without knowledge of questionnaire responses.

Data analysis

Reliability was assessed by comparison of the two lifetime histories for the exposure variables during the two time periods, birth to age 18 years and age 19 years to the time of the interview. Because of the small number of pipe and cigar smokers among parents ($n = 24$) and spouses ($n = 4$), we restricted our analysis to cigarette smokers. We summarized the per cent agreement between the first and second interviews for categorical variables, which included mother's smoking during pregnancy; mother's, father's, and spouse's cigarette smoking status; amount smoked, categorized as less than one pack per day, one pack per day, and more than one pack per day; and number of other cigarette smokers in the household, categorized as none, one, and two or more. To discount chance agreements between the first and second interviews, Cohen's kappa was calculated for all categorical items and tested for significance (7, 8). Spearman rank order correlation coefficients (9) were calculated for continuous variables, which included both the number of years and the number of hours per day that the subject's mother, father, spouse, and others had smoked.

For questions on exposure to tobacco smoke during the previous 24 hours, we created summary variables for cigarette smoke exposure only, because exposure to pipe and cigar smokers was infrequent. The summary variables for cigarette smoke exposure included the total number of hours of exposure and the total number of cigarette smokers in all locations. To examine the relation between measures of short term exposure to environmental tobacco smoke within and between interviews, we calculated Spearman rank order correlations (9).

Data analyses were performed with standard programs of the Statistical Analysis System (10).

RESULTS

Of the 158 subjects enrolled for the first interview, 149 (94 per cent) also completed the second interview. Of the nine subjects who were not reinterviewed, there were seven males and two females, with mean ages of 43.6 years and 43.0 years, respectively. This report is based on responses of those 149 subjects who were reinterviewed. The age range of the 149 subjects was 21–79 years (mean = 43 years); 37.6 per cent were males and 62.4 per cent were females (table 1). The median duration between

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interviews was 17 weeks, with a range of 6–35 weeks.

For the period birth to age 18 years, agreement between the first and second interviews was high for parental smoking status during childhood (table 2). The per cent agreement was similar for mother's and father's smoking during childhood and was lowest for maternal smoking during pregnancy. The percentage of unknown responses was highest for maternal smoking during pregnancy. The per cent agreement and kappa statistic for the number of other cigarette smokers in the home during childhood were 77.0 per cent and 0.47 ($p < 0.0001$), respectively.

In contrast to the high reliability of responses about parental smoking status during childhood, concordance was low for responses about the usual amount smoked in the home by the parents during childhood (table 3). The concordance was highest for the amount smoked by the mother and lowest for the amount smoked by the fa-

TABLE 2

Percentage of nonsmokers reporting exposure to parental cigarette smoking during childhood, New Mexico, 1986

Response	Maternal smoking during pregnancy ($n = 149$)	Maternal smoking during childhood ($n = 149$)	Paternal smoking during childhood ($n = 149$)
Yes			
First interview	20.1	36.9	55.7
Second interview	20.1	32.9	56.4
No			
First interview	67.1	62.4	43.6
Second interview	64.4	67.1	42.9
Unknown			
First interview	12.8	0.7	0.7
Second interview	15.5	0.0	0.7
Agreement			
Concordance	85.9	94.0	92.6
Kappa	0.73*	0.87*	0.85*

* $p < 0.0001$.

TABLE 3

Percentage of nonsmokers reporting exposure to various amounts of cigarettes smoked by the parents during childhood and by the spouse during adulthood, New Mexico, 1986

Amount smoked	Maternal smoking during childhood ($n = 48$)	Paternal smoking during childhood ($n = 79$)	Spousal smoking during adulthood ($n = 64$)
Less than one pack/day			
First interview	62.5	70.9	84.4
Second interview	50.0	35.4	40.6
One pack/day			
First interview	20.8	11.4	7.8
Second interview	22.9	32.9	31.3
More than one pack/day			
First interview	6.3	10.1	6.3
Second interview	16.7	22.8	28.1
Unknown			
First interview	10.4	7.6	1.6
Second interview	10.4	8.9	0.0
Agreement			
Concordance	52.1	39.3	43.8
Kappa	0.22*	0.04*	−0.04*

* $p > 0.05$.

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ther. Compared with the first interview, the percentage of subjects reporting parental smoking of one pack per day or more was higher at the second interview.

We also examined the reliability of responses on smoking status and amount smoked by sex and by age. The findings were similar to the overall analysis within strata defined by either sex or age, above and below age 40 years.

Spearman correlations were used to describe the agreement between the first and second interviews on the reported number of years and hours per day of exposure to environmental tobacco smoke during childhood. The correlation coefficients were high for responses on the number of years the parents and other smokers in the household had smoked (table 4). However, for responses on the number of hours per day of smoke exposure in the home, the correlation coefficients were much lower (table 4).

We next examined the reliability of reported smoke exposure during adulthood (tables 3 and 5). After age 18 years, the numbers of subjects living with either their mother ($n = 8$) or their father ($n = 9$) were small. For this small group of subjects, the concordance of responses on parental smoking status was 100 per cent. Similarly, the per cent agreement on spouse's smoking status, as obtained at the two interviews, was 100 per cent ($n = 67$). For the amount currently smoked by the spouse, the concordance was lower (table 3). Agreement between responses about the number of other cigarette smokers in the household

TABLE 4

Mean years and hours per day of childhood cigarette smoke exposure reported by nonsmokers, New Mexico, 1986

Exposure variable	No.	First interview	Second interview	Spearman's r
Maternal smoking				
Years*	33	15.4	15.7	0.76
Hours/day†	31	5.0	6.4	0.18
Paternal smoking				
Years	57	16.1	15.4	0.75
Hours/day	55	4.8	4.8	0.54
Other household members' smoking				
Years	28	13.9	13.2	0.63
Hours/day	20	9.2	8.4	0.51

* "During the period from birth to age 18 years, for how many years did he/she smoke cigarettes?"

† "On average, during the period from birth to age 18 years, for how many hours per day were you exposed to individuals' cigarette smoke?"

TABLE 5

Mean years and hours per day of adulthood cigarette smoke exposure reported by nonsmokers, New Mexico, 1986

Exposure variable	No.	First interview	Second interview	Spearman's r
Spouse's smoking				
Years*	40	16.2	16.4	0.96
Hours/day†	39	5.9	5.5	0.25
Other household members' smoking				
Years	67	8.3	8.2	0.78
Hours/day	58	12.7	10.3	0.54

* "For how many years did he/she smoke cigarettes while you were sharing your home?"

† "On average, how many hours per day were you exposed to their cigarette smoke?"

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was 74.0 per cent (n = 66), with a kappa value of 0.50 ($p < 0.0001$).

Correlations between responses at the two interviews were high for the number of years the spouse and other smokers in the household had smoked during the subject's adulthood, but much lower for the number of hours per day of exposure during adulthood (table 5). Because of the small number of subjects living with their parents after age 18 years, we did not calculate correlation coefficients for these variables.

Urine specimens were obtained from 98 per cent of the 149 subjects at the first interview and 95 per cent at the second interview. The median urinary cotinine levels were zero at both interviews, with mean levels of 9.2 ng/mg of creatinine at the first interview and 7.3 ng/mg of creatinine at the second interview. Cotinine levels varied widely with the total number of smokers and the total number of hours of exposure to tobacco smoke (in various situations) during the 24 hours prior to urine collection at both the first interview (figures 1 and 2) and the second interview (data not shown). The cotinine levels correlated only modestly with the questionnaire measures of exposure (table 6).

We also assessed the stability of data on exposure, as measured by questionnaire and by cotinine level (table 6). At the first

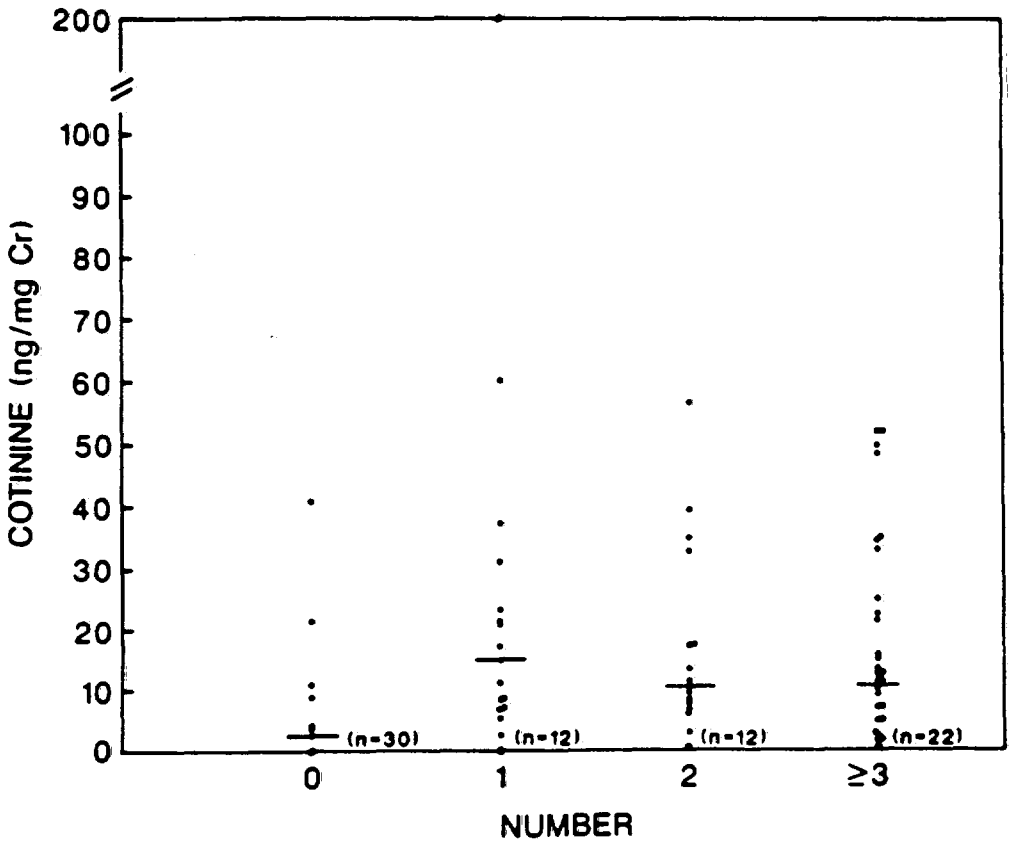

FIGURE 1. Urinary cotinine levels, standardized to urinary creatinine (Cr) concentration, among nonsmokers interviewed about tobacco smoke exposure, by the total number of cigarette smokers the subject reported being exposed to during the 24 hours prior to the first interview. Bars show the mean cotinine level for each group. Values in parentheses indicate the number of subjects with nondetectable levels of cotinine. New Mexico, 1986.

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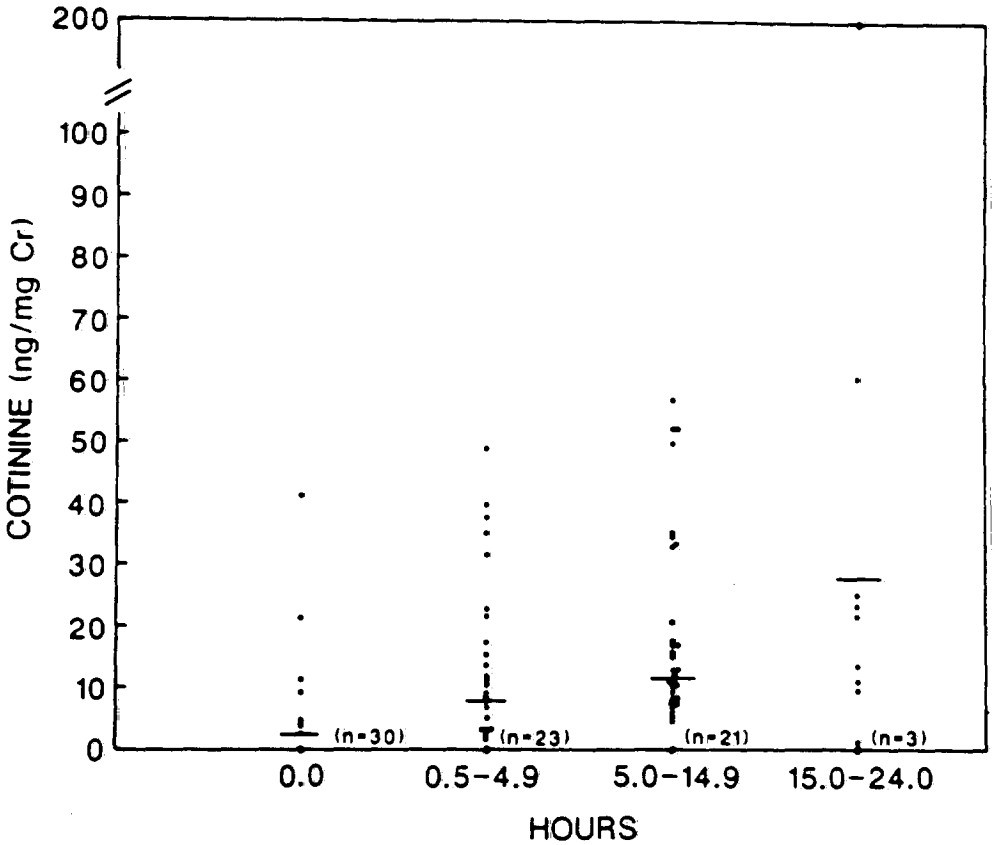

FIGURE 2. Urinary cotinine levels, standardized to urinary creatinine (Cr) concentration, among nonsmokers interviewed about tobacco smoke exposure, by the self-reported total number of hours that the subject was exposed to cigarette smoke during the 24 hours prior to the first interview. Bars show the mean cotinine level for each group. Values in parentheses indicate the number of subjects with nondetectable levels of cotinine. New Mexico, 1986.

and second interviews, the mean responses for the reported number of cigarette smokers that the subjects had been exposed to during the previous 24 hours were 2.1 and 1.8, respectively, with 20 subjects at the first interview and 22 subjects at the second interview reporting exposures in "crowds." For the total number of hours of exposure during the previous 24 hours, the mean responses at the first and second interviews were 5.1 and 4.6, respectively. Both the questionnaire variables and the cotinine data indicated a relatively stable pattern of exposure. The Spearman correlation coefficients were somewhat higher for the questionnaire-based indexes than for urinary cotinine levels.

DISCUSSION

In a group of adult nonsmokers, we found high reliability for reports on parental smoking and on smoking by others in the home (table 2) but lower reliability for semiquantitative exposure measures (tables 3–5). Mean levels of urinary cotinine increased with exposure to cigarette smoke compared with no exposure ($n = 37$) (figures 1 and 2). However, within specific levels of exposure, the cotinine levels varied widely. Across the follow-up period of sev-

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TABLE 6

Spearman correlations between measures of exposure to environmental tobacco smoke during the 24 hours prior to interview, New Mexico, 1986

Exposure variable	No.	r
Total no. of smokers to which subject was exposed		
Responses at the first and second interviews	143	0.50
Response at the first interview and cotinine level	143	0.24
Response at the second interview and cotinine level	139	0.21
Total no. of hours that subject was exposed to cigarette smoke		
Responses at the first and second interviews	144	0.62
Response at the first interview and cotinine level	145	0.32
Response at the second interview and cotinine level	138	0.29
Cotinine level		
Levels at the first and second interviews	140	0.45

eral months, exposures to environmental tobacco smoke were relatively stable, as were urinary cotinine levels (table 6). Most subjects were able to provide responses to the questions on maternal smoking during pregnancy, parental smoking during childhood, and smoking by a spouse during adulthood (tables 2 and 3).

Several limitations of these data must be considered. Because a standard for validating a lifetime history of exposure to environmental tobacco smoke is unavailable, we used repeatability as an index of the quality of questionnaire responses. We addressed the reliability of questions on lifetime exposure at home, but not in the workplace, an important source of exposure for a substantial proportion of adults (11). Interview with a volunteer subject does not replicate the usual setting of a case-control study, the design most often used to examine lung cancer and passive smoking (1). In that setting, recall bias by ill subjects may affect reliability of questionnaire responses in comparison with a volunteer population.

Similar observations on the reliability of questionnaire data on passive smoking were recently reported by Pron et al. (12). These investigators interviewed 117 subjects, controls in a case-control study of lung cancer, on two occasions separated by an average of six months. Smoking by spouses was reported with high reliability (kappa = 0.89 for both wife and husband). Repeatability was somewhat lower for smoking by the mother (kappa = 0.76) and by the father (kappa = 0.44). As in the present study, repeatability of quantitative estimates of duration of exposure was lower than for the categorical descriptions of smoking by household members.

Although neither the investigation of Pron et al. (12) nor the present study directly addresses validity of questionnaires on lifetime passive smoking, the validity of subjects' reports on smoking by parents and spouses has been described. Sandler and Shore (13) compared responses on parents' smoking given by cases and controls with responses given by the parents or siblings of the index cases. Concordance was high for whether the parents had ever smoked, although the agreement was somewhat better for smoking by the mother than for smoking by the father. Responses concerning numbers of cigarettes smoked did not agree as highly. In a follow-up study of a nationwide sample, children's responses on smoking by their deceased parents closely agreed with the information given 10 years previously by the parents themselves (14). Other studies have shown that people generally report the smoking habits of their spouses correctly (14–19). However, people's reporting of quantitative aspects of the smoking behavior of their spouses tends to be less valid (16, 18, 19).

Smoking by parents during childhood and by a spouse during adulthood represent the most important sources of household exposure to environmental tobacco smoke. The studies of subject reports for parents and spouses indicate good validity of responses on smoking by these household

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members; the study of Pron et al. (12) and the present study show that these reports are also highly reliable. Thus, exposure measures based on cigarette smoking status of parents and of spouses, as reported by an index subject, are reported with a high degree of validity and reliability, although these measures may only crudely quantitate the dose of biologically relevant tobacco smoke components. In contrast, the accuracy of more quantitative measures of smoking by these household members is lower. The resulting misclassification may explain the failure to find exposure-response relations for passive smoking and lung cancer in some studies (1, 20).

We also compared responses to questions on exposure during the previous 24 hours with urinary cotinine level. The time period for the questionnaire was limited to the previous 24 hours to reduce bias from faulty recall. However, since this period is approximately the half-life of cotinine in nonsmokers (21, 22), the cotinine level represents not only exposure during the 24 hours covered by the questionnaire but prior exposure as well.

We found modest correlations between the questionnaire-based measures of exposure and urinary cotinine levels (table 6). The level of correlation must be interpreted in the context of the different lengths of time of exposure assessed by the questionnaire and by the urinary cotinine level. Furthermore, at a given level of nicotine exposure, urinary cotinine level is also influenced by uptake, metabolism, and excretion, which are likely to vary among individuals.

Coultas et al. (23) found that questionnaire measures of household exposure were not strong predictors of salivary cotinine level. In 247 adult nonsmokers with a detectable cotinine level, the subject's age, the number of cigarettes smoked per day by the spouse, and the number of cigarettes smoked per day by other smokers in the household explained only 2 per cent of the variance in cotinine levels for females and 16 per cent of the variance for males. Even in active smokers, questionnaire responses on smoking behavior do not tightly predict cotinine concentrations in body fluids (24–27). Higher correlations between urinary cotinine levels and reported exposure to cigarette smoke have been reported for young children (28). The higher correlations in the studies of young children probably reflect the time-activity patterns in this age group (29); parental smoking in the household is generally the dominant source of exposure.

In adults, the weak relation between cotinine level and reported smoke exposure implies that a single cotinine measurement should not be used to estimate exposure for individuals (23). However, in our subjects, cotinine levels varied among exposure groups (figures 1 and 2), suggesting that cotinine measurements might be used as an index of mean exposure for members of a particular exposure group.

Nonsmokers are exposed to environmental tobacco smoke in many different environments, including the home, the workplace, and other private and public locations. Since subjects in an epidemiologic investigation cannot be expected to comprehensively describe the extent of exposure in each of these environments, misclassification of the amount of exposure to environmental tobacco smoke must be anticipated from the use of questionnaires. However, subjects can provide valid and reliable reports concerning the smoking status of household members. The combination of questionnaires and biologic markers offers a feasible approach for assessing recent exposure to environmental tobacco smoke.

References

1. US Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, 1986. (DHHS (CDC) publication no. 87-8398).
2. National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: National Academy Press, 1986. (ISBN 0-309-03730-1).
3. Centers for Disease Control. Cigarette smoking in

2023381477

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the United States, 1986. MMWR 1987;36:581–5.
4. Samet JM, Coultas DB, Howard CA, et al. Respiratory diseases and cigarette smoking in an Hispanic population in New Mexico. Am Rev Respir Dis 1988;137:815–19.
5. Langone JJ, Gjika HB, Van Vunakis V. Nicotine and its metabolites: radioimmunoassays for nicotine and cotinine. Biochemistry 1973;12:5025–30.
6. Faulkner WR, King JW. Renal function. In: Tietz NW, ed. Fundamentals of clinical chemistry. Philadelphia, PA: WB Saunders Co, 1976:975–1014.
7. Fleiss JL. Measuring nominal scale agreement among many raters. Psychol Bull 1971;76:378–82.
8. Maclure M, Willett WC. Misinterpretation and misuse of the Kappa statistic. Am J Epidemiol 1987;126:161–9.
9. Colton T. Statistics in medicine. Boston, MA: Little, Brown and Company, 1974.
10. SAS Institute, Inc. SAS user's guide: statistics. Version 5 edition, 1985. Cary, NC: SAS Institute, Inc, 1985.
11. Friedman GD, Petitti DB, Bawol RD. Prevalence and correlates of passive smoking. Am J Public Health 1983;73:401–5.
12. Pron GE, Burch JD, Howe GR, et al. The reliability of passive smoking histories reported in a case-control study of lung cancer. Am J Epidemiol 1988;127:267–73.
13. Sandler DP, Shore DL. Quality of data on parents' smoking and drinking provided by adult offspring. Am J Epidemiol 1986;124:768–78.
14. McLaughlin JK, Dietz MS, Mehl ES, et al. Reliability of surrogate information on cigarette smoking by type of informant. Am J Epidemiol 1987;126:144–6.
15. Rogot E, Reid D. The validity of data from next-of-kin in studies of mortality among immigrants. Int J Epidemiol 1975;4:51–4.
16. Kolonel LN, Hirohata T, Nomura AMY. Adequacy of survey data collected from substitute respondents. Am J Epidemiol 1977;106:476–84.
17. Pershagen G. Validity of questionnaire data on smoking and other exposures with special reference to environmental tobacco smoke. Eur J Respir Dis 1984;133(suppl):76–80.
18. Humble CG, Samet JM, Skipper BE. Comparison of self- and surrogate-reported dietary information. Am J Epidemiol 1984;119:86–98.
19. Lerchen ML, Samet JM. An assessment of the validity of questionnaire responses provided by a surviving spouse. Am J Epidemiol 1986;123:481–9.
20. Humble CG, Samet JM, Pathak DR. Marriage to a smoker and lung cancer risk. Am J Public Health 1987;77:598–602.
21. Kyerematen GA, Damiano MD, Dvorchik BH, et al. Smoking-induced changes in nicotine disposition: application of a new HPLC assay for nicotine and its metabolites. Clin Pharmacol Ther 1982;32:769–80.
22. Sepkovic DW, Haley NJ, Hoffmann D. Elimination from the body of tobacco smoke products by smokers and passive smokers. (Letter). JAMA 1986;256:863.
23. Coultas DB, Howard CA, Peake GT, et al. Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. Am Rev Respir Dis 1987;136:305–9.
24. Benowitz NL, Hall SM, Herning RI, et al. Smokers of low-yield cigarettes do not consume less nicotine. N Engl J Med 1983;309:139–42.
25. Abrams DB, Follick MJ, Biener L, et al. Saliva cotinine as a measure of smoking status in field settings. Am J Public Health 1987;77:846–8.
26. Lee PN. Lung cancer and passive smoking: association an artefact due to misclassification of smoking habits? Toxicol Lett 1987;35:157–62.
27. Pierce JP, Dwyer T, DiGuisto E, et al. Cotinine validation of self-reported smoking in commercially run community surveys. J Chronic Dis 1987;40:689–95.
28. Greenberg RA, Haley NJ, Etzel RA, et al. Measuring the exposure of infants to tobacco smoke. N Engl J Med 1984;310:1075–8.
29. Harlos DP, Marbury M, Samet J, et al. Relating indoor NO_2 levels to infant personal exposures. Atmosph Environ 1987;21:369–76.

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REFERENCES

1. Sacks JJ, Smith JD, Kaplan KM, Lambert DA, Sattin RW, Sikes RK: The epidemiology of injuries in Atlanta day care centers. JAMA 1989;262:1641–1645.
2. US Consumer Product Safety Commission: A handbook for public playgrounds safety. Volume I: General guidelines for new and existing playgrounds. Washington, DC:US CPSC, 1986.
3. Aronson SS, Aiken LS: Compliance of child care programs with health and safety standards: Impact of program evaluation and advocate training. Pediatrics 1980; 65:318–325.
4. Hogan P: The playground safety checker. A checklist approach to risk management. Phoenixville, PA: Playground Press, 1988.
5. Werner P: Playground injuries and voluntary product standards for home and public playgrounds. Pediatrics 1982; 69:18–20.
6. Landman PF, Landman GB: Accidental injuries in children in day care centers. Am J Dis Child 1987;141:292–293.
7. Chang A, Lugg MM, Nebedum A: Injuries among preschool children enrolled in day care centers. Pediatrics 1989; 83:272–277.
8. Aronson SS: Injuries in child care. Young Child Sept 1983; 19–20.
9. Boyce WT, Sobolewski S, Sprunger LW, Schaefer C: Playground equipment injuries in a large, urban school district. Am J Public Health 1984; 74:984–986.
10. Centers for Disease Control: Playground-related injuries in preschool-aged children—United States, 1983–1987. MMWR 1988; 37:629–632.
11. Reichelderfer TE, Overbach A, Greensher J: Unsafe playgrounds. Pediatrics 1979; 64:962–963.
12. Sweeney TB: X-rated playgrounds? Pediatrics 1979; 64:961.
13. Sweeney TB: Playgrounds and head injuries: A problem for the school business manager. School Business Affairs Jan 1987; 28–31.
14. Fisher L, Harris VG, VanBuren J, Quinn J, DeMaio A: Assessment of a pilot child playground injury prevention project in New York State. Am J Public Health 1980; 70:1000–1002.
15. Davis WS, McCarthy PL: Safety in day care centers (Abstract) Am J Dis Childhood 1988; 142:386.

A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke

DAVID B. COULTAS, MD, JONATHAN M. SAMET, MD, JOHN F. MCCARTHY, ScD, AND JOHN D. SPENGLER, PhD

Abstract: We enrolled 15 nonsmoking volunteers to evaluate the feasibility of measuring personal exposure to environmental tobacco smoke (ETS) at work and to characterize workplace exposures. During one workshift, we obtained questionnaires on exposure, saliva and urine for cotinine, and personal air samples for respirable particles and nicotine. The levels of cotinine, respirable particles, and nicotine varied widely with self-reports of exposure to ETS, but on average increased with increasing exposure. (*Am J Public Health* 1990; 80:988–990.)

Introduction

While health effects of passive smoking on children and adults have been identified, the principal location of exposure investigated has been the home.[1,2] Workplace exposure has received less attention, and health effects of environmental tobacco smoke (ETS) in the workplace remain controversial.

We enrolled 15 nonsmoking adults to determine the feasibility of measuring personal exposure to ETS at work and to characterize workplace exposures of this small group of subjects. Indicators of exposure, measured during a workday, included questionnaires, personal samples for respirable particles (RSP) and nicotine, and urinary and salivary cotinine.

Methods

Between October 1986 and May 1987, 15 nonsmoking volunteers (eight men, seven women), 18 years of age and older, were recruited from the Albuquerque, New Mexico area. We obtained exposure questionnaires, saliva, urine, and personal air particle samples during one workshift. The saliva and urine specimens were obtained before and after the workshift. Cotinine was quantitated by a double antibody radioimmunoassay, as described by Langone, *et al.*[3] Details of the assay in our laboratory have been reported previously.[4]

During the workshift, each subject wore a personal monitoring pump running at 1.7 l/min with a 10 mm nylon cyclone clipped to the shirt collar.[5] RSP samples were collected on 37 mm Fluropore filters (Millipore Corp). Nicotine was collected on a glass fiber backup filter treated with sodium bisulfate to minimize volatilization; after extraction from the filter, analysis for nicotine was done on a gas chromatograph with a flame ionization detector.[6] The recovery of nicotine by this procedure has been shown to be 98 percent efficient.

From the questionnaires, we derived measures of exposure including the total number of cigarette smokers and total number of hours exposed during the workshift. To describe the relationships among the measures of ETS exposure, Spearman correlations were calculated. Data analysis was performed with standard programs.[7]

Results

Occupations of the subjects were diverse (Table 1); mean age was 44.8 years; average duration of the workshift and of the personal monitoring was 6.5 hours (SD ± 2.0).

Exposure to cigarette smokers at work was reported by 13 of the 15 participants. Of the 13 reporting exposure, two reported exposure to crowds of smokers during their workshift and the remaining 11 encountered a mean of 8.8 smokers (SD ± 6.7). The mean reported hours of exposure was 3.4 (SD ± 2.1).

Respirable particle and nicotine concentrations varied widely with the reported number of smokers and hours of exposure. The mean concentrations for RSP and nicotine were 63.9 $\mu g/m^3$ (SD ± 41.5) and 20.4 $\mu g/m^3$ (SD ± 20.6), respectively. Correlations between the atmospheric markers

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TABLE 1—Description of Participants in a Personal Monitoring Study of Exposure to Environmental Tobacco Smoke at Work, New Mexico, 1986–87

Occupation/Workplace	Workshift Duration/ Exposure Duration (hours)	RSP ($\mu g/m^3$)	Nicotine ($\mu g/m^3$)
Males			
Physician/Hospital	8/5	52.3	10.0
Social Worker/Office	8/0	44.0	2.5
Stock Broker/Office	8/2	69.4	7.2
Bus Boy/Restaurant	8/8	145.8	45.0
Maintenance Worker/Retail Store	8/3	85.2	6.9
Barber/Barber Shop	8/0	14.7	4.0
Barber/Barber Shop	8/4	145.8	13.7
Volunteer/Hospital	4/2	80.0	46.0
Females			
Interviewer/Public Transportation	3/2	4.0	0.0
Travel Agent/Office	8/5	85.7	50.0
Travel Agent/Office	8/4	62.1	46.7
Attorney/Office	8/6	83.3	5.9
Volunteer/Hospital	4/3	27.6	6.3
Volunteer/Hospital	4/3	25.2	8.7
Volunteer/Hospital	4/4	53.2	53.2

and the questionnaire measures of exposure to ETS were moderate (Table 2).

As was observed for the atmospheric markers, the post-workshift urinary and salivary cotinine levels varied widely with self-reported exposure. In comparison with pre-workshift levels, post-workshift levels were not consistently increased. The mean pre-workshift urinary and salivary cotinine concentrations were 31.8 ng/mg Cr (SD ± 67.6) and 2.9 ng/ml (SD ± 5.0), respectively. For the post-workshift levels, the corresponding values were 19.7 ng/mg Cr (SD ± 43.2) and 3.5 ng/ml (SD ± 5.9).

Spearman correlation coefficients were calculated to examine the relations among the questionnaire variables, the atmospheric markers, and urinary and salivary cotinine (Table 2). Moderate correlations were obtained for self-reports and cotinine levels, and nicotine levels and cotinine levels. However, RSP levels and cotinine concentrations were not correlated.

TABLE 2—Spearman Correlations between Various Measures of Environmental Tobacco Smoke at Work, New Mexico, 1986–87

Correlated Measures	N	r
RSP ($\mu g/m^3$) with:		
Nicotine	15	0.57*
Total number of smokers	15	0.44
Total hours of exposure	15	0.53*
Postshift urinary cotinine	14	0.05
Postshift salivary cotinine	11	−0.07
Nicotine ($\mu g/m^3$) with:		
Total number of smokers	15	0.62*
Total hours of exposure	15	0.54*
Postshift urinary cotinine	14	0.60*
Postshift salivary cotinine	11	0.48
Postshift urinary cotinine (ng/mg Cr) with:		
Total number of smokers	14	0.39
Total hours of exposure	14	0.57*
Postshift salivary cotinine (ng/ml) with:		
Total number of smokers	11	0.63*
Total hours of exposure	11	0.45

*$p < 0.05$

Discussion

The controversial effects of involuntary smoking in the workplace need further investigation. The conduct of such research would be facilitated by the development of unintrusive and accurate methods of exposure assessment. Alternative approaches include active and passive monitoring, biological markers, and questionnaires. We have shown that personal monitoring for tobacco smoke components can be accomplished in the workplace. However, many employers and employees would not participate in the study because of concern about the wearing of pumps.

Despite the small number of subjects studied in this investigation, objective evidence of exposure to ETS was obtained in various workplaces. The levels of RSP and nicotine were similar to those observed in other investigations.[6,8–10] However, few of these studies included information on the intensity and duration of exposure to ETS.[10]

We observed moderate positive correlations among the questionnaire measures of ETS exposure, the results of personal monitoring for RSP and nicotine, and measurements of urinary cotinine. Each of these types of measures provides a differing index of exposure to ETS.[1] The questionnaire measures that were used assess source strength, but concentrations of ETS are also influenced by room volume and ventilation. Nicotine is a specific marker of exposure to ETS, whereas RSP is nonspecific. Cotinine levels reflect nicotine exposure, but also are determined by timing of specimen collection[10] and uptake and metabolism. Thus, tight concordance among these broad indicators of exposure used in this study would not be anticipated.

Because of the differing characteristics of questionnaires, personal monitoring, and biological markers for assessing ETS exposure, no single method should be considered as optimal for studying the workplace. We recommend that assessment of ETS exposure in indoor environments should utilize multiple approaches to characterize short- and long-term exposures. In population studies, questionnaire measures of exposure offer the simplest approach with personal atmospheric markers and biologic markers providing methods for estimating the potential magnitude of misclassification of self-reported exposure.

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REFERENCES

1. US Department of Health and Human Services: The Health Consequences of Involuntary Smoking: A Report of the Surgeon General. (DHHS [CDC] pub. no. 87-8398). Rockville, MD: US Public Health Service, 1986.
2. National Research Council: Environmental Tobacco Smoke. Measuring Exposures and Assessing Health Effects. Washington, DC: National Academy Press, 1986.
3. Langone JJ, Gjika HB, Van Vunakis H: Nicotine and its metabolites. Radioimmunoassays for nicotine and cotinine. Biochemistry 1973; 12:5025–5030.
4. Coultas DB, Howard CA, Peake GT, Skipper BJ, Samet JM: Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. Am Rev Respir Dis 1987; 136:305–309.

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5. Turner WA, Spengler JD, Dockery DW, Colome SD: Design and performance of a reliable monitoring system for respirable particulates. J Air Pollut Control Assoc 1979; 29:747–748.
6. Hammond SK, Leaderer BP, Roche AC, Schenker M: Collection and analysis of nicotine as a marker for environmental tobacco smoke. Atmospher Environ 1987; 21:457–462.
7. SAS Institute, Inc: SAS User's Guide: Statistics. Version 5 edition. Cary, NC: SAS Institute, Inc, 1985.
8. Spengler JD, Treitman RD, Tosteson TD, Mage DT, Soczek ML: Personal exposure to respirable particulates and implications for air pollution epidemiology. Environ Sci Technol 1985; 19:700–707.
9. Muramatsu M, Umemura S, Okada T, Tomita H: Estimation of personal exposure to tobacco smoke with a newly developed nicotine personal monitor. Environ Res 1984; 35:218–227.
10. Mattson ME, Boyd G, Byar D, Brown C, Callahan JF, Corle D, Cullen JW, Greenblatt J, Haley NJ, Hammond K, Lewtas J, Reeves W: Passive smoking on commercial airline flights. JAMA 1989; 261:867–872.

Sexual Histories of Heterosexual Couples with One HIV-Infected Partner

NANCY S. PADIAN, MPH, PHD

Abstract: Ninety-eight heterosexual couples enrolled in a HIV transmission study, at least one of whom was HIV-infected, were interviewed about sexual behavior. Although males and females were interviewed separately, there was agreement between them on the number of sexual contacts, the practice or anal intercourse, and condom use. These findings of strong reliability are encouraging, but do not necessarily imply that the data are valid. (*Am J Public Health* 1990; 80:990–991.)

Introduction

The best way to prevent the spread of infection from human immunodeficiency virus (HIV) is voluntary behavioral change.[1] Before recommending strategies to promote such changes, one must first establish the kinds of behavior currently practiced. To do so, AIDS (acquired immunodeficiency syndrome) researchers rely almost exclusively on interviewing techniques, but many question the validity and reliability of this methodology.[2] For example, in a study of the reproductive histories of a group of women, Hornsby and Wilcox[3] established that daily logs of sexual behavior were more accurate than comparable data collected through retrospective interviews. Similar results were found by both Udry and Morris[4] and Kunin and Ames,[5] who determined that recent and frequent reporting of sexual behavior produced the most precise results. However, AIDS epidemiologists may not have the opportunity to collect data on a regular basis and are thus forced to rely on retrospective reports of behavior even though the accuracy of these reports (especially for a variety of sexual practices) has not been established. Here I report on the reliability of such data, comparing reports of sexual behavior between men and women in couples of which at least one partner was HIV seropositive.

Methods

Since 1985 we have been conducting a study of the heterosexual transmission of acquired immunodeficiency syndrome (AIDS) in California in which we enroll the opposite sex partners of individuals infected with HIV. Although the study began by enrolling the female partners of HIV-infected men,[6] in 1987 we began to enroll participants as couples. Individuals who test positive for HIV at a variety of sites and who also have heterosexual partners are referred to the study as part of their post-test counseling. Enrollment is voluntary; study protocol is described elsewhere.[6]

Interviewers are female and are matched to couples by ethnicity. They are trained in group and individual sessions that include role playing and interpretation of interview responses. Results were reliable across interviewers. To ascertain number of sexual contacts, the interviewer asks how many times the couple has sexual intercourse in a typical week or month. Deviations from this number throughout the relationship are noted. The total number of contacts is estimated by multiplying the duration of the relationship by the typical reported amount and weighting this number by changes in sexual activity over time. Individuals in the couple are interviewed separately on the same day.

Behaviors considered in this report are: vaginal intercourse, anal intercourse, and condom use. Continuous responses were compared using Pearson's correlation coefficient, and categorical responses were compared using the Kappa coefficient and its corresponding confidence limits as described by Fleiss.[7] HIV infection was ascertained from serological tests using enzyme immunoassays with Western Blot confirmation.

Results

This report includes data from 98 couples, 68 percent of which were monogamous at entry into the study. Most of the men and women reported only one partner in the six months prior to entry into the study. Median number of partners since 1978 (the beginning of the AIDS epidemic) was five for the women and 10 for the men. The overall male-to-female transmission rate from the study which began in 1985 was 24 percent. Seventy-seven of the couples included infected men and their female partners; 12 (16 percent) of these women were infected. Twenty-one of the couples were infected women and their male partners; none of these men were infected. The reported risk group of the infected partner of the 98 couples varied and is described in Table 1. Sixty-three percent of the couples were White, 20 percent Latino, 7 percent Black, 1 percent Asian, and the remainder were couples of mixed ethnicity. Average income for the couples was $20–29,000 per year; average level of education was 13

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Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home[1-4]

DAVID B. COULTAS,[5] JONATHAN M. SAMET, JOHN F. MCCARTHY, and JOHN D. SPENGLER

SUMMARY: We assessed the variability of four markers of environmental tobacco smoke exposure in 10 homes with 20 nonsmoking and 11 smoking household members. We obtained exposure questionnaires, saliva and urine for cotinine, and air particle samples for respirable particles and nicotine on 10 sampling days: every other day over 10 days, and then 1 day every other week over 10 wk. The mean concentrations of respirable particles in the 10 homes ranged from 32.4 to 78.9 μg/m³, and concentrations of nicotine ranged from 0.6 to 6.9 μg/m³. Linear regression models that included indicator variables for self-reported exposure explained 9 and 6% of the variability of the respirable particle and the nicotine concentrations, respectively. The individual mean urinary cotinine levels standardized to creatinine concentration ranged from 3.9 to 55.8 ng/mg Cr, and for salivary cotinine the mean levels ranged from 0.9 to 4.3 ng/ml. Indicator variables for self-reported exposure explained 8 and 23% of the variability of the urinary and salivary cotinine levels, respectively. We conclude that because of the marked variability of these measures, multiple measurements are needed to establish a stable profile of exposure to environmental tobacco smoke in the home.

AM REV RESPIR DIS 1990; 142:602-606

Introduction

Numerous epidemiologic investigations have examined the adverse effects of passive smoking on children and adults; the evidence is sufficiently compelling to establish passive smoking as a cause of disease in nonsmokers (1, 2). Both the 1986 Surgeon General's Report (1) and the National Research Council (2) have concluded that passive smoking causes increased lower respiratory illness in infants, increased respiratory symptoms in children, reduced lung growth during childhood, and lung cancer in nonsmokers. Although health effects of passive smoking have been convincingly demonstrated, additional research is needed to address unresolved issues concerning this preventable exposure. For example, more precise description of exposure-response relations should be achieved for the already established health effects. Uncertainties concerning the adverse effects of passive smoking in the workplace and on the occurrence of ischemic heart disease must also be resolved.

The conduct of this research would be facilitated by improved methods for exposure assessment. In most epidemiologic studies on passive smoking published to date, exposure to environmental tobacco smoke, the combination of exhaled mainstream smoke and sidestream smoke, has been assessed by questionnaire. However, exposure to environmental tobacco smoke can also be estimated with air monitoring and measurement of biologic markers in body fluids, such as salivary cotinine. Biologic markers are increasingly emphasized as a standard for validating questionnaire responses. To characterize the relationships among these alternative approaches for assessing passive smoking in the home environment, we conducted a prospective study of 10 households. We periodically collected questionnaire information on exposure and measured respirable particles and nicotine in air samples and urinary and salivary cotinine in the 20 nonsmokers in these households.

Methods

Sample Selection

Between February and December 1986, 149 nonsmoking volunteers, 18 years of age and older, were recruited from Albuquerque and surrounding communities to participate in a study of the accuracy of questionnaire assessment of exposure to environmental tobacco smoke (3). From this sample, we selected 10 subjects living with at least one cigarette smoker and requested the participation of the entire household for this investigation. The households were selected on the basis of willingness to participate and location, and were not intended to be representative of the original sample.

Data Collection

Between March and October 1986, we obtained exposure questionnaires, saliva and urine, and air particle samples on 10 sampling days: every other day over 10 days, and then 1 day every other week over 10 wk. The questionnaires and saliva and urine specimens were obtained at the end of a 24-h air monitoring period (described below). From the questionnaires, we determined the reported number of smokers and number of hours that the subjects were exposed during the previous 24 h to cigarettes, cigars, and pipes at home, at work or school, in a vehicle, and in other places. Questionnaires were self-completed by the adults, and by a parent for children 14 years of age and younger. Spot saliva and urine specimens were obtained and frozen at −20° C until the cotinine assays were performed.

Cotinine Assay

Cotinine was quantitated by a double antibody radioimmunoassay, as described by Langone and coworkers (4). A specific antiserum produced in rabbits was supplied by Dr. Helen Van Vunakis (Brandeis University). Urine samples were diluted 1:4 for the assay. The sensitivity of the assay in our hands was 36 pg/tube or 0.78 ng/ml of urine (4,204 pmol/L). Urine creatinine concentrations were determined by the Jaffe reaction (5), and the cotinine concentrations were standardized to the creatinine concentrations. Assays were performed without knowledge of questionnaire responses.

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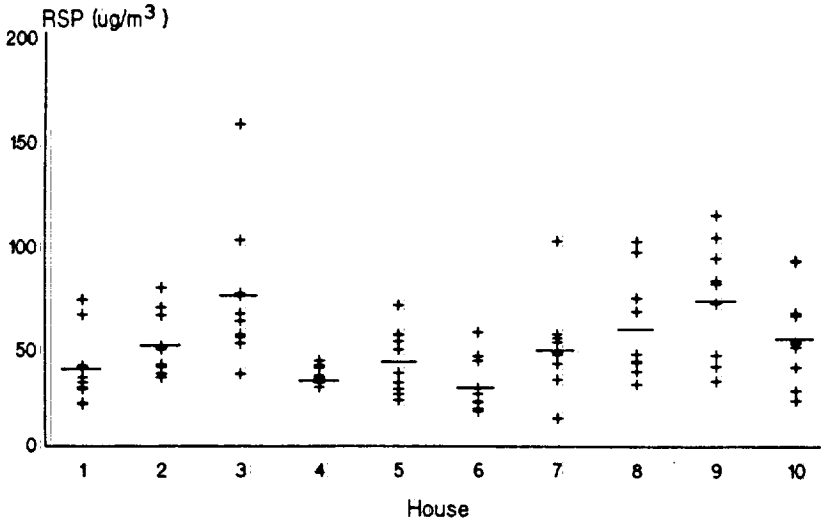

Fig. 1. Respirable particle concentrations (RSP) measured during 24-h sampling periods in 10 homes with at least one cigarette smoker. The bars indicate the mean levels for each home.

Particle Measurements

In the major activity room of each home, Harvard School of Public Health impactors (6), operating at a flow rate of 4 L/min, were used to collect respirable particles and gaseous nicotine samples. Through a timed solenoid switching valve, two impactors used a common, mass-flow controlled pump, and each impactor operated on alternate 15-min collection cycles. Respirable particle samples, 2.5 μm in diameter or less, were collected on Teflon® filters (Membrana, Inc., Pleasanton, CA), and nicotine was collected on sodium-bisulfate-treated glass fiber filters (Millipore Corp., Bedford, MA) to minimize its volatilization. After extraction from the filter, analysis for nicotine was done on a Shimadzu GC7A gas chromatograph (Columbia, MD) with a flame ionization detector. The nicotine collection and extraction procedure is a modification of that described by Hammond and coworkers (7). The recovery of nicotine by this procedure has been shown to be 98% efficient. The sensitivity for detection of respirable particles and nicotine was 5.0 μg and 0.05 ppm, respectively.

Data Analysis

Variability of questionnaire responses, respirable particle and nicotine concentrations, and urinary cotinine levels were assessed with univariate analyses. From the questionnaire responses, we used the total number of household smokers, including cigarette, cigar, and pipe smokers, and the total number of hours exposed as the measures of home exposure. The predominant source of tobacco smoke was from cigarette smoking. During the entire sampling period, there were only 4 days in which any subject reported exposure to a cigar smoker, and none reported exposure to a pipe smoker.

To examine determinants of the variability in the measurements, we used multiple linear regression. The dependent variables (respirable particles, nicotine, urinary cotinine, and salivary cotinine) were analyzed as continuous variables. For the predictive factors, indicator variables were defined for house (HOUSE = 1 to 10), individual (INDIVIDUAL = 1 to 20), age group (AGE GROUP < 18 yr versus ≥ 18 yr), season (SEASON = March–April versus May–October), and number of smokers per day (NUMBER = zero versus ≥ 1). Other independent variables, number of hours (HOURS) exposed per day, respirable particles, and nicotine were continuous.

Data analyses were performed with standard programs of the Statistical Analysis System (8).

Results

The 10 households included 11 cigarette smokers and 20 nonsmokers, 11 females and nine males 1.5 to 74 yr of age. The homes included eight unattached single family houses, one mobile home, and one apartment.

Reports on exposure to tobacco smoke in the home were obtained for all 10 sampling days from 17 subjects, and for 9 days from three subjects. The reported number of cigarette smokers in the home per day did not vary widely. The median number (range) of smokers per day was one for 18 of the nonsmoking subjects (zero to 10), zero for one subject (zero to 1), and four for one subject (2 to 25). Greater variability was reported for the number of hours exposed to cigarette smoke in the home, with the median number of hours ranging from zero to 11 h.

Respirable particle and nicotine concentrations were obtained for 99% of the sampling days (figures 1 and 2). The mean concentrations of respirable particles in the 10 homes ranged from 32.4 μg/m³ (SD = 13.1) to 76.9 μg/m³ (SD = 32.9), and concentrations of nicotine ranged from 0.6 μg/m³ (SD = 0.69) to 6.9 μg/m³ (SD = 8.2). Spearman's correlation coefficient between the respirable particle concentrations and the nicotine concentrations was 0.54 (n = 99, p = 0.0001).

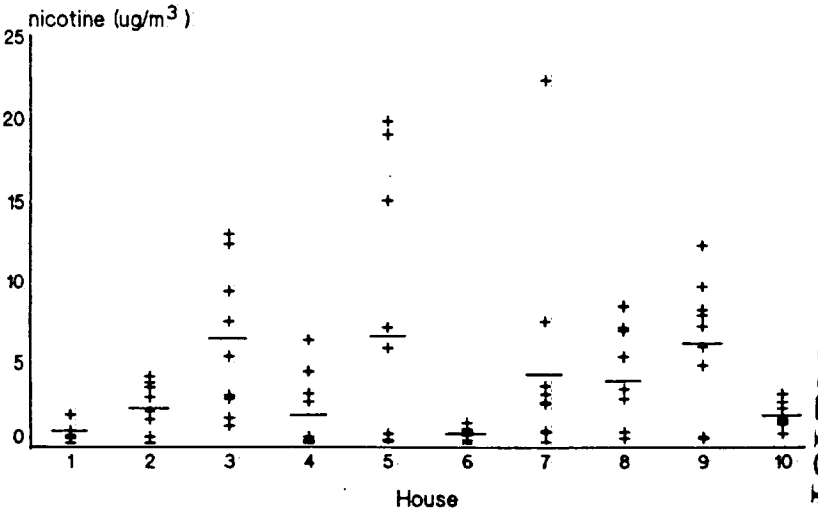

Fig. 2. Atmospheric nicotine concentrations measured during 24-h sampling periods in 10 homes with at least one cigarette smoker. The bars indicate the mean levels for each home. Levels of nicotine were undetectable on 1 or more days in Houses 1 (n = 3), 2 (n = 2), 4 (n = 2), and 8 (n = 1).

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TABLE 1

COEFFICIENTS OF DETERMINATION FOR THREE LINEAR REGRESSION MODELS* PREDICTING RESPIRABLE PARTICLE AND NICOTINE CONCENTRATIONS IN AIR SAMPLES FROM 10 HOMES, NEW MEXICO, 1986

	R^2		
Dependent Variable	Model 1	Model 2	Model 3
Respirable particles, μg/m³	0.34	0.08	0.09
Nicotine, μg/m³	0.28	0.04	0.06

* Independent variables: Model 1 = HOUSE (1 to 10, representing the 10 homes); Model 2 = NUMBER (zero versus ≥ 1 smokers) + SEASON (March–April versus May–October); Model 3 = NUMBER (zero versus ≥ 1 smokers) + HOURS (continuous) + SEASON (March–April versus May–October).

TABLE 2

REGRESSION COEFFICIENTS FOR MODEL THREE* PREDICTING RESPIRABLE PARTICLE AND NICOTINE CONCENTRATIONS IN AIR SUPPLY FROM 10 HOMES, NEW MEXICO, 1986

	Regression Coefficients for Model 3		
	One or More Smokers	HOURS	Cold Months
Respirable particles, μg/m³	+17.3 (−3.0, 37.7)†	+0.4 (−1.0, 1.8)	+8.9 (−1.1, 18.9)
Nicotine, μg/m³	+2.1 (−2.7, 5.9)	+0.2 (−0.1, 0.5)	−0.7 (−2.5, 1.1)

* See text and table 1 for description of Model 3.
† 95% confidence intervals shown in parentheses.

The variability of respirable particle and nicotine concentrations for the two sampling periods, every other day or every other week, were described with one-way analysis of variance. For the respirable particle concentrations, the intra-house mean square error, describing the extent of variation for a particular household, was greatest for sampling every other day (516.8) compared with every other week (258.7). A contrasting pattern of variation was observed for nicotine, with mean square errors of 3.6 and 19.0 for every other day and every other week, respectively.

For the particle and nicotine measurements, we used linear regression to examine factors influencing the concentrations and the variability of the concentrations. A model that included variables representing each of the 10 houses explained the greatest amount of variability, as shown by the magnitude of the R^2 value (table 1). Compared with the model with the variables for individual homes, the models that included number of smokers explained markedly lower percentages of the variability of levels of nicotine and particles. Although not statistically significant, increases in respirable particles were associated with exposure to one or more cigarette smokers in the home and with the colder months, March and April (table 2). There was no association of particle levels with the number of hours of exposure. Nicotine levels increased, although not significantly, with exposure to smokers in the home, but were not predicted by the season (table 2).

Cotinine levels were obtained on 187 urine specimens from 20 nonsmokers, and 153 saliva specimens were obtained from 16 nonsmokers. We were unable to obtain saliva specimens from four children, all 4 yr of age or younger. The individual mean urinary cotinine levels standardized to urinary creatinine concentration ranged from 3.9 ng/mg Cr (SD = 6.5) to 55.8 ng/mg Cr (SD = 32.0). For salivary cotinine, the mean levels ranged from 0.9 ng/ml (SD = 0.8) to 4.3 ng/ml (SD = 1.4). The mean urinary cotinine levels and variability tended to be greater in the children than in the adults (figures 3 and 4) (data not shown for salivary cotinine). Spearman's correlation between the urinary cotinine and salivary cotinine concentrations was 0.32 (n = 153, p = 0.0001). Correlations between the cotinine levels and the atmospheric markers were highest for salivary cotinine and nicotine (table 3).

As for the atmospheric markers, we

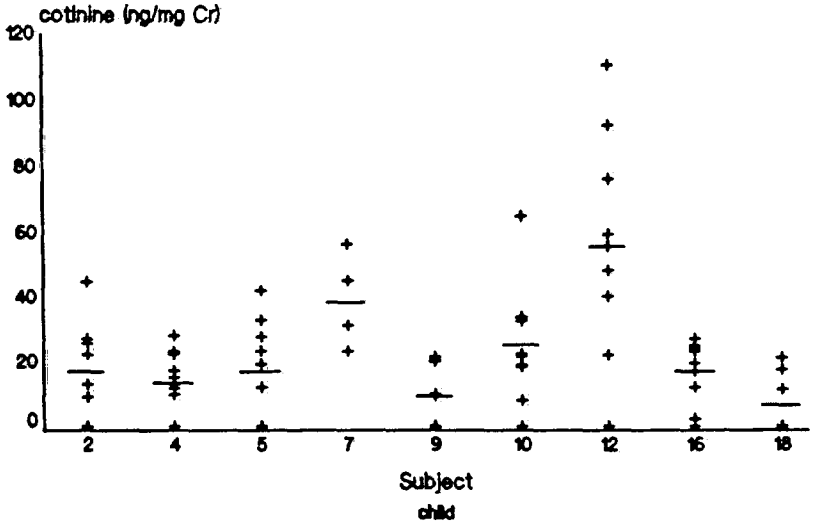

Fig. 3. Urinary cotinine concentrations standardized to urinary creatinine concentration in nine nonsmoking children from homes with at least one cigarette smoker. The bars indicate the mean levels for each child. Levels of urinary cotinine were undetectable on 1 or more days for Subjects 2 (n = 2), 4 (n = 2), 5 (n = 3), 9 (n = 4), 10 (n = 1), 12 (n = 1), 16 (n = 1), and 18 (n = 5).

TABLE 3

SPEARMAN'S CORRELATION COEFFICIENTS BETWEEN COTININE LEVELS IN URINE AND SALIVA AND RESPIRABLE PARTICLES AND NICOTINE, NEW MEXICO, 1986

	r
Urinary cotinine, n = 187	
Respirable particles	0.25
Nicotine	0.15
Salivary cotinine, n = 153	
Respirable particles	0.25
Nicotine	0.38

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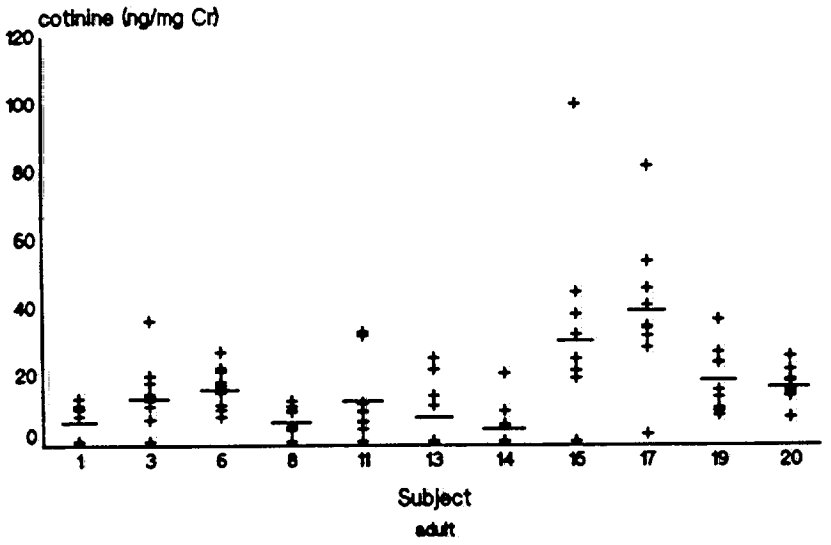

Fig. 4. Urinary cotinine concentrations standardized to urinary creatinine concentration in 11 nonsmoking adults from homes with at least one cigarette smoker. The bars indicate the mean levels for each adult. Levels of urinary cotinine were undetectable on 1 or more days for Subjects 1 (n = 4), 3 (n = 2), 8 (n = 2), 11 (n = 1), 13 (n = 6), 14 (n = 6), and 15 (n = 2).

TABLE 4

COEFFICIENTS OF DETERMINATION FOR THREE LINEAR REGRESSION MODELS* PREDICTING URINARY AND SALIVARY COTININE CONCENTRATIONS IN NONSMOKERS EXPOSED TO TOBACCO SMOKE, NEW MEXICO, 1986

	R^2		
Dependent Variable	Model 1	Model 2	Model 3
Urinary cotinine, ng/mg Cr	0.47	0.05	0.08
Salivary cotinine, ng/ml	0.57	0.09	0.23

* Independent variables: Model 1 = INDIVIDUAL (1 to 20, representing the 20 nonsmoking individuals); Model 2 = NUMBER (zero versus ≥ 1 smokers) + SEASON (March–April versus May–October) + AGE GROUP (< 18 versus ≥ 18 yr); Model 3 = NUMBER (zero versus ≥ 1 smokers) + HOURS (continuous) + SEASON (March–April versus May–October) + AGE GROUP (< 18 versus ≥ 18 yr).

used one-way analysis of variance to describe the variability in urinary and salivary cotinine concentrations during the two sampling periods: every other day or every other week. In contrast to the atmospheric markers, the variability in cotinine levels was comparable for the two periods. The intraindividual mean square errors for urinary cotinine were 175.8 and 194.8, and for salivary cotinine it was 0.9 and 0.7.

For the urinary and salivary cotinine levels, we also examined determinants of variability and concentration with linear regression. Models that included indicator variables for the 20 nonsmoking subjects explained 47 and 57% of the variability in cotinine levels, respectively (table 4). Compared with this model, other models that included exposure to environmental tobacco smoke and age group explained much lower proportions of the variability. Urinary cotinine levels were significantly ($p < 0.05$) higher among children than among adults (table 5). Although the effect was not significant, exposure to one or more smokers resulted in higher urinary cotinine levels than did no exposure. The number of hours of reported exposure and the season were not significant predictors of cotinine level. For salivary cotinine level, the hours of exposure was the only significant predictor.

Prediction of level of urinary or salivary cotinine was not greatly improved with the use of respirable particles or nicotine as independent variables. The proportions of the variability in the urinary cotinine levels explained by respirable particle and nicotine concentrations were 0.03 and 0.04, respectively. For salivary cotinine, the corresponding R^2 values were only slightly higher at 0.07 and 0.13, respectively.

Discussion

Environmental tobacco smoke is a complex mixture of gases and particles that changes as it ages. Personal exposure to environmental tobacco smoke is determined by the nonsmoker's activity pattern; exposure may be received in the diverse microenvironments encountered throughout the course of day-to-day activities. For many nonsmokers, the home is a predominant location of exposure (9). In this investigation, we assessed methods for measuring exposure to environmental tobacco smoke in the home that can be used for epidemiologic research: air monitoring, questionnaires, and biologic markers.

In other populations, cigarette smok-

TABLE 5

REGRESSION COEFFICIENTS FOR MODEL THREE* PREDICTING URINARY AND SALIVARY COTININE CONCENTRATIONS IN NONSMOKERS EXPOSED TO TOBACCO SMOKE, NEW MEXICO, 1986

	Regression Coefficients* Model 3			
	One or More Smokers	HOURS	SEASON	AGE GROUP
Urinary cotinine, ng/mg Cr	+5.4 (−4.8, 15.6)†	+0.8 (0.0, 1.6)	−0.2 (−5.8, 5.4)	+5.4 (0.0, 10.8)
Salivary cotinine, ng/ml	+0.13 (−0.06, 0.86)	+0.15 (0.09, 0.21)	−0.02 (−0.41, 0.37)	−0.81 (−1.34, −0.28)

* See text and table 4 for description of Model 3.
† 95% confidence intervals shown in parentheses.

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ing has been shown to be a strong source of respirable particles in the home (1, 10, 11). Spengler and coworkers (10) estimated that the average increase in the indoor concentration of respirable particles was 20 $\mu g/m^3$ for each smoker. We estimated an average increase of 17 $\mu g/m^3$ for one or more smokers (table 2); the average concentrations in the New Mexico homes (figure 1) were above the mean of 24 $\mu g/m^3$ in nonsmoking homes from six U.S. cities (10). Nicotine was present on most sampling days (figure 2). The moderate correlation between the nicotine and respirable particle concentrations (Spearman's $r = 0.54$) confirms the importance of tobacco smoking as a source of particulate pollution in the home. Little data have been reported on nicotine concentrations in the home (1, 2); the levels in the New Mexico homes were somewhat lower than an average concentration of 11.2 $\mu g/m^3$ reported by Muramatsu and coworkers (12) for three homes in Japan. However, the results from our investigation and the Japanese study are not directly comparable because the Japanese data were from personal samples. Furthermore, information on intensity or duration of exposure to tobacco smoke was not provided for the Japanese homes. In a recent study in North Carolina, the homes of 27 children were monitored overnight for nicotine with a sampler that was located near the child (13). The average nicotine concentration in homes with smokers was 3.74 $\mu g/m^3$, with a range from about 1 to 7 $\mu g/m^3$. The higher levels in our study may reflect the differing sampling strategies; the nicotine sampler remained in the activity room throughout the monitoring period in our study, but it was moved to the child's bedroom in the North Carolina study when the child slept.

Questionnaires on exposure to environmental tobacco smoke generally assess the strength of the source, e.g., the number of smokers or the number of cigarettes consumed, and the duration of exposure. The concentration of environmental tobacco smoke, however, depends not only on the source strength but on room size, mixing, adsorption of smoke components, and the rate of exchange of indoor with outdoor air. Personal exposure also varies with the nonsmoker's proximity to the smoker. Questionnaires cannot comprehensively and accurately assess each of these factors.

Not surprisingly, we found that the questionnaire responses were poor predictors of concentrations of respirable particles and nicotine (table 1). The highest R^2 values were obtained with a regression model that included variables for the individual homes; presumably, these variables represented characteristics of the homes, many of them unmeasurable, that determined concentrations at a given level of smoking.

Cotinine, nicotine's major metabolite, has a half-life of 20 to 40 h in nonsmokers (1). It can serve as a specific biologic marker of exposure to environmental tobacco smoke that has been received over a period of days. At any given level of nicotine exposure, cotinine levels in body fluids are also determined by uptake, metabolism, and excretion (1). In regression analyses to predict cotinine concentrations, the models that included variables for the individual subjects gave the highest R^2 values (table 4). Models including only the questionnaire-derived exposure measures or the atmospheric markers had low R^2 values. Our findings in a large population-based survey were similar (14). In 247 nonsmoking adults with a detectable cotinine level, variables for subject age, number of cigarettes smoked by the spouse, and number of cigarettes smoked by other household smokers explained only 2% of the variance of salivary cotinine level for females, and 16% of the variance for males.

In epidemiologic investigations of the adverse health effects of environmental tobacco smoke, questionnaires have been the sole approach for assessing exposure (1, 2). Air monitoring and biologic markers represent promising and feasible approaches for assessing exposure to environmental tobacco smoke. For the home environment, our data demonstrate that indexes of exposure to environmental tobacco smoke based on questionnaires, biologic markers, and air monitoring are not tightly correlated. At a particular level of exposure, as assessed by inventory of household smokers, concentrations of respirable particles and nicotine vary widely, as do levels of salivary and urinary cotinine. The variability of the atmospheric and biologic markers must be considered in using them as standards for assessing misclassification by questionnaires. For environmental tobacco smoke exposure at home, our data suggest that single measurements of either levels of environmental tobacco smoke components or of biologic markers are not adequate for characterizing usual exposure. Multiple measurements are needed. It may be misleading to assess the validity of questionnaire measures against a single determination of an atmospheric or biologic marker. We suggest that atmospheric and biologic markers offer complementary approaches to questionnaires for assessment of exposure to environmental tobacco smoke, and that these methods should be used together to estimate the magnitude of misclassification from questionnaire responses.

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References

1. U.S. Department of Health and Human Services. The health consequences of involuntary smoking, a report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, 1986. (DHHS publication no. [CDC] 87-8398).
2. National Research Council. Environmental tobacco smoke. Measuring exposures and assessing health effects. Washington, DC: National Academy Press, 1986.
3. Coultas DB, Peake GT, Samet JM. Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. Am J Epidemiol 1989; 130:338-47.
4. Langone JJ, Gjika HB, Van Vunakis H. Nicotine and its metabolites. Radioimmunoassays for nicotine and cotinine. Biochemistry 1973; 12: 5025-30.
5. Faulkner WR, King JW. Renal function. In: Tietz NW, ed. Fundamentals of clinical chemistry. Philadelphia: W. B. Saunders, Co., 1976; 975-1014.
6. Turner WA, Marple VA, Spengler JD. Indoor aerosol impactor. In: Liu BYH, Pui D, Fissan H, eds. Aerosols. New York: Elsevier Science Publishing Co., 1984; 527.
7. Hammond SK, Leaderer BP, Roche AC, Schenker M. Collection and analysis of nicotine as a marker for environmental tobacco smoke. Atmos Environ 1987; 21:457-62.
8. SAS Institute, Inc. SAS user's guide: Statistics. 5th ed. Cary, NC: SAS Institute, Inc., 1985.
9. Friedman GD, Petitti DB, Bawol RD. Prevalence and correlates of passive smoking. Am J Public Health 1983; 73:401-5.
10. Spengler JD, Dockery DW, Turner WA, Wolfson JM, Ferris BG Jr. Long-term measurements of respirable sulfates and particles inside and outside homes. Atmos Environ 1981; 15:23-30.
11. Brunekreef B, Boleij JSM. Long-term average suspended particulate concentrations in smokers' homes. Int Arch Occup Environ Health 1982; 50:299-302.
12. Muramatsu M, Umemura S, Okada T, Tomita H. Estimation of personal exposure to tobacco smoke with a newly developed nicotine personal monitor. Environ Res 1984; 35:218-27.
13. Henderson FW, Reid HF, Morris R, *et al.* Home air nicotine levels and urinary cotinine excretion in preschool children. Am Rev Respir Dis 1989; 140:197-201.
14. Coultas DB, Howard CA, Peake GT, Skipper BJ, Samet JM. Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. Am Rev Respir Dis 1987; 136:305-9.

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References

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1. Tannenbaum SR, Bryant MS, Skipper PL, Macclure M (1986) Hemoglobin adducts of tobacco-related aromatic amines: application to molecular epidemiology. In: Mechanisms in tobacco carcinogenesis, Banbury Report #23, Cold Spring Harbor Laboratories, New York
2. Svendsen KH, Kuller LH, Martin MJ, Ockene JK (1987) Effects of passive smoking in the multiple risk factor intervention trial. Am J Epidemiol 126:783–795
3. Sandler DP, Helsing KJ, Comstock GW (1987) Heart disease mortality in persons living with smokers. In: Proceedings of the 4th International Conference on Indoor Air, Berlin
4. Harlap S, Davies AM (1974) Infant admissions to hospital and maternal smoking. Lancet 1:529–532
5. Committee on Passive Smoking, National Research Council (1986) Environmental tobacco smoke: measuring exposures and assessing health effects. National Academy Press, Washington DC, p 243
6. Ferris BG, Ware JH, Berkey CS, et al (1985) Effects of passive smoking on health of children. Environ Health Perspect 62:289–295

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Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?

P. N. Lee

Summary

Combined evidence from at least 15 epidemiological cohort and case-control studies appears to indicate non-smokers married to smokers have a risk of lung cancer 30%–40% higher than that of non-smokers married to non-smokers. This increase is surprisingly large, given the very low level of exposure to smoke constituents of non-smokers compared with that of smokers. The possibility that it results wholly or in part from bias, rather than as a direct effect of exposure to environmental tobacco smoke (ETS), must be considered seriously. Weaknesses of much of epidemiological evidence and the various possible sources of bias are discussed in detail.

One serious potential source of bias arises if even a small proportion of smokers are misclassified as non-smokers. Data from a series of studies specifically designed to determine accuracy of statements on current smoking habits (by salivary cotinine measurements) and on past smoking habits by repeated questionnaires) suggests that such misclassification might cause bias large enough to explain a major part, and perhaps all, of the apparent increase in lung cancer risk related to spouse smoking. Whilst evidence from a detailed review of the available literature on misclassification of smoking habits, is consistent with this view, there is a need for more research on this issue. Future epidemiological studies on passive smoking and lung cancer need to obtain more objective and reliable information on the subject's smoking habits and exposure to ETS. Bias can also arise if positive studies are more likely to be reported than negative studies and research is needed to attempt to estimate the extent of this bias.

Data currently available do not permit reliable conclusions to be drawn concerning the relationship of ETS exposure to lung cancer risk.

The Association

Since the early studies of Hirayama (1981) and Trichopoulos et al. (1981) reporting that never smokers married to smokers have a higher risk of lung cancer than those married to non-smokers, further epidemiological evidence has accumulated. Table 1 summarizes evidence from 16 published studies, 1–3 being prospective studies and 4–16 case-control studies. Wald et al. (1986), based on results from studies 1–13, reported an overall significant relative risk of 1.35, with 95% confidence limits of 1.19–1.54. This estimate is in broad agreement with other estimates of 1.30 (Lee 1984), 1.41 (Wells 1986) and 1.2–1.5 (Doll 1986). It would not be materially affected by including results from studies 14–16 of Table 1 since they are all small, and have relative risks that vary either side of the average.

While the overall evidence, which is based on a total of almost 1,200 lung cancer deaths in never smokers, predominantly in females, suggests a statistically significant

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Table 1. Summary of epidemiological studies of risk of lung cancer in never smokers in relation to environmental tobacco smoke exposure

Study number	Authors	Study location	Sex	Number of lung cancers[a]	Relative risk	Significance[b]
1	Hirayama (1981, 1984)	Japan	F	163	1.63	Yes
			M	64	2.25	Yes
2	Garfinkel (1981)	USA	F	153	1.17	No
3	Gillis et al. (1984)	Scotland	F	8	1.00	No
			M	6	3.25	No
4	Trichopoulos et al. (1981, 1983)	Greece	F	77	2.11	Yes
5	Chan and Fung (1982)	Hong Kong	F	84	0.75	No
6	Correa et al. (1983)	USA	F	22	2.07	(Yes)
			M	8	2.00	No
7	Buffler et al. (1984)	USA	F	41	0.78	No
			M	11	0.52	No
8	Kabat and Wynder (1984)	USA	F	24	0.79	No
			M	12	1.00	No
9	Koo et al. (1984, 1987)	Hong Kong	F	88	1.64	No
10	Garfinkel et al. (1985)	USA	F	134	1.31	(Yes)
11	Akiba et al. (1986)	Japan	F	94	1.50	No
			M	19	1.80	No
12	Lee et al. (1986)	England	F	32	1.00	No
			M	15	1.30	No
13	Pershagen et al. (1987)	Sweden	F	67	1.20	No
14	Wu et al. (1985)	USA	F	29	1.20	No
15	Ziegler (in Delager et al. (1986))	USA	M	16	<1	No
16	Humble et al. (1987)	USA	F	20	1.80	No
			M	8	>1.80	No

[a] Among never smoking subjects
[b] Yes = significant at 95% confidence level in comparison of exposed and non-exposed subjects; (Yes) = significance only in trend analysis or in subjects exposed to heavy smokers

association, it is not at all clear that it represents a causal effect of exposure to environmental tobacco smoke.

Before coming to any conclusion it is necessary to consider two important questions:

(a) Is the magnitude of the association plausible, in view of what is known about the epidemiology of active smoking and the relative levels of smoke constituents to which smokers and non-smokers are exposed?

(b) Is the epidemiological evidence open to any serious bias which might affect relative risk estimates in specific studies, or generally?

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Table 2. Comparison of relative risks of lung cancer in relation to passive and active smoking

Study number	Authors	Sex	Relative risk		Ratio of excess risk
			Passive	Active	
1	Hirayama (1981, 1984)	F	1.63	3.81	0.22
		M	2.25	4.91	0.32
3	Gillis et al. (1984)	F	1.00	1.53	0.00
		M	3.25	5.92	0.46
4	Trichopoulos et al. (1981, 1983)	F	2.08	2.90	0.57
5	Chan and Fung (1982)	F	0.75	3.07	−0.12
6	Correa et al. (1983)	F	2.07	18.51	0.06
		M	2.00	18.27	0.06
7	Buffler et al. (1984)	F	0.78	5.37	−0.05
		M	0.52	5.26	−0.11
9	Koo et al. (1984, 1987)	F	1.64	3.80	0.23
11	Akiba et al. (1986)	F	1.50	3.36	0.21
		M	1.80	3.55	0.31
12	Lee et al. (1986)	F	1.00	4.75	0.00
		M	1.30	12.91	0.03
14	Wu et al. (1985)	F	1.20	4.50	0.06

Plausibility

Table 2 compares relative risks of lung cancer in relation to passive and active smoking. The passive smoking estimates compare risk in never smokers according to whether or not they are married to a smoker, while the active smoking estimates compare ever smokers and never smokers. Exceptionally, in studies 1 and 3, the comparison is in relation to current rather than ever smoking. The table also shows the ratio of excess risk in relation to passive and active smoking. Nine of the 16 ratios suggest an effect of passive smoking 6% or less than that of active smoking, while seven suggest an effect 20% or more. Overall the epidemiological data appear to be indicating that passive smoking has 10–15% of the effect of active smoking. Most studies of active smoking suggest a linear relationship between lung cancer risk and number of cigarettes smoked per day, though a quadratic relationship has been proposed (Doll and Peto 1978). It follows that if the epidemiological data are unbiased one would expect that the average dose received from passive smoking is at least 10%–15% of that from active smoking.

Many workers have used the (virtually) tobacco specific marker cotinine as an indicator of exposure of passive and active smokers. Table 3, based on an extensive UK study by Lee (1987) which will be referred to in more detail below, found that the increase in salivary cotinine in relation to passive smoking was less than 1% of that in relation to active smoking. Similar findings have been reported by other workers (e.g. Jarvis et al. 1984). The only study reporting relative levels much higher than this (Matsukura et al. 1984) has been questioned (Adlkofer et al. 1985; Pittenger 1985).

Since lung cancer risk in smokers is generally thought to be related to particulate matter rather than nicotine, it can be argued that an index of relative exposure of passive

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Table 3. Salivary cotinine levels in relation to active and passive smoking

Exposure	Sex	Salivary cotinine (ng/ml)		
		Exposed	Non-exposed	Differences
Active smoking	M	319.2	0.85	318.3
	F	310.6	0.40	310.2
Spouse smoking (among non-smokers)	M	2.9	0.6	2.3
	F	1.0	0.3	0.7
Ratio of differences		Male 0.7%		
		Female 0.2%		

Table 4. Smoking related particulate levels in US smokers and non-smokers

Measure	Sex	Smoking related particulates (mg/day)		
		Active smoker	Non-smoker	Ratio
Inhaled dose	M	477.3	0.63	0.1%
	F	366.5	0.30	0.1%
Retention		80%	11%	
Retained dose	M	381.8	0.069	0.02%
	F	293.2	0.033	0.01%

and active smokers based on particulate matter would be more relevant. Table 4, based on Arundel et al. (1986), gives estimates for the US population of relative inhaled and retained particulate matter doses of non-smokers and active smokers. The ratios in Table 4 have to be adjusted upwards by a factor of 2 or 3 to make them comparable with the data in Tables 2 and 3, since (see Table 3) the difference between exposed and non-exposed non-smokers is two to three times the average level of non-smokers. This brings the inhaled dose estimates broadly in line with the cotinine estimates, though the retained dose estimates are about an order of magnitude lower. The lower figure for retained particulate matter is based on the work of Hiller et al. (1982a,b) who found that the collection efficiency of particles in environmental tobacco smoke is 11%, in contrast to the substantially higher figure of 80% for mainstream smoke. Robins (1986) also calculated that non-smokers take in the equivalent of an extremely small number of cigarettes per day in terms of respirable particulates. He noted that estimates of cigarette equivalents based on cotinine may be misleadingly high, since, whereas nicotine is in the particulate phase in mainstream smoke and will be absorbed mainly through the lungs, nicotine in ETS is mainly in the vapour phase, and, being water soluble, can be absorbed through the mucous membranes without ever reaching the lungs.

There appears to be a *huge discrepancy*, of two or perhaps three orders of magnitude between the claimed relative effects of passive and active smoke exposure and the much smaller relative exposure of passive and active smokers. What might explain this huge discrepancy?

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One might argue that studies of active smoking, by including exposed and non-exposed non-smokers in their comparison group, underestimate the effect of active smoking so that the ratios in Table 2 are too high.

This is irrelevant for three reasons:

(a) the comparison between Tables 2 and 3 is in fact direct and not affected by this false baseline problem,
(b) failure to take the false baseline into account would have virtually no effect if risk was proportional to exposure and exposures in passive smokers are so low and
(c) it ignores a bias in the opposite direction due to failure to take into account the fact that smokers obviously have greater passive smoke exposure than do non-smokers.

Another point to be considered is duration of smoking. Since, in active smokers, risk of lung cancer is approximately related to the 4th power of duration of smoking (Doll and Peto 1978), one might infer that failure to take account of differences in duration might cause relative bias by a factor of 3.2 ($= 60_4/45_4$) when comparing a 60 year old non-smoker exposed to passive smoke from birth and a 60 year smoker who started at age 15. Actually, the relative bias will be much less than this for two reasons. First, by no means all passive smokers will have been exposed since birth. Second, the "duration to a power" formula is only a valid approximation at smoker doses. Assuming a multistage model, it can easily be shown that at low doses the excess risk in relation to passive smoking becomes approximately linearly related to duration of smoking.

Neither of the above points really affect the huge discrepancy for which an explanation is being sought. If one is still wishing to accept the epidemiology as valid, one would have to seek an explanation either in a greater toxicity of ETS than mainstream smoke or in a greater susceptibility of non-smokers. While there is evidence that sidestream smoke has higher concentrations of some toxic chemicals than mainstream smoke, the relevance of this finding to environmental tobacco smoke which is aged, vastly diluted, chemically altered sidestream smoke, is not at all clear. There does not appear to be any direct evidence that ETS is particularly noxious. Nor is there any direct evidence that active smoking reduces susceptibility to relevant effects of ETS.

Limitations of Epidemiology

While it is not possible to completely rule out such explanations, the obvious alternative explanation – that the epidemiology is in some way biassed – seems on the face of it much more plausible. While the claimed effect of passive smoking may be large when viewed against the magnitude of effect predicted on dosimetric grounds, it is actually quite small when viewed against the magnitude of effect it has proved possible in the past to reliably identify using epidemiological methods. Alderson (1983) has suggested that a well designed case-control study should be able to confirm a two fold difference in risk but that, for differences less than this, the power of the study design may be inadequate. While case-control studies are particularly susceptible to a variety of sources of potential bias, this conclusion may well be true for any non-randomised epidemiological study (Lee 1988a).

In trying to assess whether bias might have arisen in the epidemiological evidence it is necessary to consider potential limitations of the available data. A number of general points can be made:

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EPIDEMIOLOGY: ITS SCOPE AND LIMITATIONS FOR INDOOR AIR QUALITY

by KARL UBERLA

Prof. Dr. Med. Karl Uberla, born in 1935, studied medicine and psychology at the Universities of Heidelberg, Munich, Innsbruck and Freiburg. He got his M.D. in 1960 at Freiburg and his master's degree in psychology in 1962. From 1962 to 1963 he was visiting associate professor at the Department of Psychology at the University of Illinois. He worked as Research Assistant at the Institute fur Medizinische Statistik und Dokumentation of the University of Mainz. After his completing habilitation thesis in 1968 he got the chair as professor of medical statistics and data processing at Ulm. He served there as dean of the medical faculty and as vice president of the University. Since 1973 he has the chair of Medical Informatics, Biometry and Epidemiology at the University of Munich. During 1981-1985 he served as President of the Federal Health Office, Berlin. He has published more than 200 scientific articles on topics in Epidemiology, Biometry, Medical Data Processing, Risk Evaluation and Public Health.

Science is inherently controversial, particularly when it reaches its thresholds. Specifically, this is the case with low risk associations based on epidemiologic and toxicologic evidence. Examples of low risk associations in the control of indoor air quality are formaldehyde, asbestos, radon and "passive smoking". When SNOW in Great Britain analysed the association between cholera and water supply in the last century by epidemiologic methods, the relative risk was much larger. Today we are mainly concerned with low risk associations.

In my paper I will first address the scope of epidemiology and some of its basic limitations. In the second part I will deal with a case study of pas-

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sive smoking. Does passive smoking cause lung cancer? What is the contribution of epidemiology to this question? Such a case study provides a fair idea of the problems in low risk estimation by epidemiologic and toxicologic methods.

Toxicology and epidemiology are partners in the assessment of risks. Toxicology ascertains whether a risk in man can exist. Epidemiology ascertains whether there is a risk in man and what the size of the risk is. The relation between toxicologic methods and epidemiologic methods is important. On what line of thought should we rely? From a scientific point of view toxicologic data can only show whether there can be a risk in man. Epidemiologic methods alone can show whether there really is such a risk in man and what the magnitude of such a risk is. The latter cannot be inferred from toxicology data.

1. THE SCOPE OF EPIDEMIOLOGY

There are some twenty definitions of epidemiology, which vary to some extent. I use here the definition by MACMAHON (1970): Epidemiology is the study of the distribution and determinants of disease frequency in man. This definition -like others- contains, on the one hand, the distribution of diseases and health in populations, the descriptive part of epidemiology. On the other hand, it contains the search for the causes and determinants of diseases, implemented by analytic epidemiology. Epidemiology has a rich history. It uses nowadays complicated statistical models. Descriptive and analytic methods both contribute to the evidence.

Epidemiology starts from available data. Widely used data are vital records and death certificates, morbidity surveys, data from disease notification and registration and dedicated studies. Basic characteristics of persons are used in epidemiologic studies. Such characteristics are age, sex, race and nationality, marital status, occupation and socioeconomic status. There are a host of other variables to be considered, but experience has shown that these are important for most studies.

Epidemiology studies the variation in time. Variation in time can hint at the factors underlying diseases. There are point epidemics, which are limited to space and time. There are secular changes and cyclic fluctuations and there exist sometimes clusters in time. Variations in place are very im-

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portant to epidemiology. Differences in disease frequencies between countries can be partly attributed to socioeconomic and other differences between nations. International comparisons are therefore a useful instrument. Also the variation within a country can be an important source of our knowledge. The study of migrant populations -for instance the diseases of Japanese immigrants and their offsprings in the United States- offers an especially interesting source of epidemiologic evidence.

There are various study types in epidemiology. To make things simple I mention only two basic ones: cohort studies and case control studies. In cohort studies one starts in the present and observes into the future. In a defined group of people the exposure is assessed -for instance with environmental tobacco smoke (ETS)- and the lung cancer cases are observed in the following years. When performed properly such studies give good evidence. They need large numbers and are expensive. One can estimate incidences from such studies, one can estimate relative risks and one can also ascertain the attributable risk.

Case-control studies start with the cases and for every case one or several "controls" are selected. In both groups one tries to assess the exposure from history. This implies certain weaknesses. One can calculate a so-called odds ratio from such studies, which is an approximation of the relative risk in the case of low risk. One has to be careful in interpreting such studies for a variety of reasons. They are disturbed by bias, that is, systematic error. The memory is very susceptible to modifications of the reality. The controls might not be fair, confounders cannot be excluded and so on. However, case-control studies are not so expensive. One often has no other choice than to rely on the weaker evidence provided by such studies.

I want to mention three problems. Bias is a systematic error, which can occur in all epidemiologic studies. It is basically defined by the difference between the true value and its estimator. There are various sources and types of bias, for instance selection bias, interviewer bias and so on. Confounding means that the exposure-disease relationship is mixed up with the effects of extraneous variables. If such variables are observed, confounding can be controlled for, at least in principle. Misclassification means that a person is wrongly counted in a certain group, when he or she belongs to another group. A systematic trend in misclassification is called differential misclassification, which can give rise to wrong estimates of relative risk.

We use three different risk measures in epidemiology: incidence, rela-

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tive risk and attributable risk. The incidence is the ratio of those getting a disease or experiencing an event during a certain time span in relation to those at risk. The relative risk is the ratio of two incidences: the incidence in those with a defined risk and the incidence in those without the risk. The relative risk is independent of the size of the incidence. So it does miss an important part of the information on the risk. Another risk measure is the attributable risk. It is a difference of incidences: the incidence of those under risk minus the incidence of those without risk. Basically this is the number of additional deaths which are caused by the exposure in a defined population. The attributable risk can only be used when one knows that there is a causal relation between exposure and event. Otherwise the attributable risk is a speculation. One must stress that these three risk measures should not be used separately. They are connected by definition and they should be viewed together since each of them contains only part of the information on risk.

A statistical association does not imply a causal relation. One has to keep this in mind. A statistically significant association is from the very beginning fictitious. It has often nothing to do with causal connection. We had for instance in our country during a certain time a statistically significant association between the number of nests of storks and the number of babies born, which clearly is an artifact. Causal influence is approached by exclusion of other explanations. There are well-known criteria which must be fulfilled in their majority, if one wants to infer a causal connection between exposure and effect from epidemiologic data. These criteria for a causal inference from epidemiologic studies were proposed by Bradford-Hill and have been modified. They are criticized nowadays by some epidemiologists. Only a few causal connections remain acceptable when one sticks to these criteria. They are very basic and can be relied upon. They surely are acceptable to scientifically oriented persons. However, they should not be used like a simple checklist:

- There should be consistency of association in the available studies.
- The results should be similar in the same circumstances and should be replicable.
- The strength and the intensity of an association is an indicator for causality. A causal connection is less probable with a low relative risk of 2 than with a high relative risk of 5 or 10.

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- There should be specificity of association. Exposure, effect and way of action should be specific. This means that the exposure and the effect must be measured in a reliable and valid way.
- There should be a dose-response relationship. With higher doses there should be larger effects, at least in a certain dose range.
- The temporal relation between exposure and event should be such that the effect can be caused by the exposure. In cancer the latency period between exposure and event is 15 years and longer.
- Bias and confounding should be carefully excluded.
- There should be an impact of intervention. Removing the exposure should lead to a reduction of the risk, as was the case in the British doctors' study on the cessation of smoking and lung cancer.
- Finally, there should be biological plausibility.

Applying those criteria, one usually ends with limited or inadequate evidence. The International Agency of Research on Cancer (5) has used those criteria and proposed four levels of epidemiologic evidence in cancer research:

1. Sufficient evidence of carcinogenicity. There is a causal relationship between the exposure and human cancer.
2. Limited evidence of carcinogenicity. A causal interpretation is credible; however, alternative explanations (such as chance, bias and confounding) cannot be adequately excluded.
3. Inadequate evidence. There are few pertinent data or the available studies, while showing evidence of association, do not exclude chance, bias or confounding.
4. No evidence. Several adequate studies are available which do not show evidence of carcinogenicity.

Epidemiology as far as it is a science should adhere to stringent criteria. Otherwise it will become the playing ground for time-dependent opinions and prejudices. It is as honest to adhere to the null hypothesis as it is honest to accept the alternative hypothesis. In science the proof of the alternative hypothesis relies on those who propose it. In regulation one has to act before one knows exactly. This difference between knowledge and action is important. As scientists, we should not act before we know at least something.

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2. SOME BASIC LIMITATIONS IN EPIDEMIOLOGY.

In epidemiology we are concerned with complicated questions. As in other sciences, there are serious limitations.

A first limitation is that adequate studies are usually not available. In most cases one ends up with very limited data with respect to the hypothesis in question. Epidemiologic studies, if properly conducted, take a long time. So data are missing and adequate evidence is not available.

Often the validity of the exposure and of the endpoint measures is low. Proxy variables are used, which might not correlate well with what we intend to measure.

Adequate studies need huge numbers and consequently are very costly. There are many important questions and only a very small part of them can be investigated. Epidemiologic research has to be centered on a few questions. In our time, the important questions are questions of low risk associations. The high risks -smoking, infections and so on- have been studied and can be studied easily when new problems arise. When the effect is small in comparison to chance, bias and confounding, we are in trouble.

In addition, there are conflicting group interests in all societies. Consequently, studies can be financed or not, can be interpreted in different ways and can be brought to the attention of the public and the legislative bodies or not. Scientists in epidemiology must stay independent, for instance from industry and from public pressure groups, sometimes even from governmental agencies. As scientists we have to rely on clear facts and not on opinion.

As in other sciences there are thresholds for human perception and knowledge in epidemiology. There are mainly two reasons for such thresholds: in order to recognize a small risk, one needs huge numbers. Random noise creeps in. We simply cannot observe one million people over 20 years without dropouts, losses and missing data. So the results are not reproducible. On the other hand we have to live in case-control studies with bias and confounding. Therefore, relative risks smaller than 2 are generally difficult to reproduce. They are then beyond the threshold of human perception and knowledge. Incidences smaller than 10^{-5} to 10^{-6} can usually not be reproduced in cohort studies. They are then beyond the threshold of human perception and knowledge.

There are also thresholds for human perception in toxicology. Inferring from animal to man is such a threshold. In toxicology we have the paradigm

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of a missing threshold for carcinogenic substances. However, this paradigm is disputed more and more. A single molecule does not always meet its receptor and a single radiation quant does not always hit a target. So there must be cases in which there is an individual threshold. Furthermore there are repair mechanisms at nearly every level of carcinogenesis. For promotors the paradigm of a missing threshold has already been modified. In my opinion, the concept of a missing threshold for initiators will also disappear and will be replaced by more sophisticated models.

3. PASSIVE SMOKING AND LUNG CANCER: A SHORT CASE STUDY

There is no doubt that active smoking can cause lung cancer. Mainstream smoke contains a variety of carcinogens. A very high percentage, 90-95%, of lung cancer cases are smokers. A wealth of epidemiologic evidence shows a high risk increase with active smoking. There is hardly another single behavior which could be changed -like stopping smoking- which would have a comparable beneficial effect on the health and life expectancy of exposed populations. Stopping alcohol consumption could produce a beneficial effect of the same size order. Therefore, it is reasonable to try to reduce the exposure to carcinogens by active smoking, as it is reasonable to try to reduce the exposure to alcohol.

Lung cancer rates have been increasing in most countries since the beginning of the century when lung cancer was a very rare disease. The rates are much lower among women. During the last decades lung cancer has also increased among women. The most important risk factor for lung cancer is active smoking. Other risk factors are asbestos, radon, tuberculosis or genetic factors, but they are less important. DOLL and PETO estimate that about 90% of the lung cancer cases in men can be attributed to active smoking. Lung cancer leads to death in a very short time. One year after diagnosis only about 33 % still live, after five years only 10%. When lung cancer is diagnosed, the fatal destiny goes on.

There is very little known about the exposure of non-smokers to ETS. We looked at it in a representative sample in 1983 in Germany (7). Non-smoking men are exposed 1.20 hours a day in the working place, non-smoking women 0.40 hours. Considering only working non-smokers, men are

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exposed 2.00 hours a day, women 1 hour per day, that is 8.3 and 4.3 percent of the total time. One has to consider that only 42% of the population are never-smokers in our country and that the real values are lower due to the method of data collection.

The question is whether passive smoking causes lung cancer. There are other unhealthy effects of passive smoking, like cardiovascular effects, bronchopulmonary effects in children and effects on the unborn child during pregnancy. I restrict myself to the case of passive smoking and lung cancer. The National Research Council (9) and the Surgeon General of the United States (10) have stated that there is or there might be a causal relationship. Also, the German Research Foundation followed this path, which is mainly based on reasoning by analogy.

The best available study is the study of HIRAYAMA (2,3,4). I will try to show how weak the evidence from this study is. The original data are given in Table 1.

TABLE 1: SMOKING HABIT OF HUSBAND BY AGE OF WIFE. ORIGINAL DATA.

WIVES	HUSBAND'S SMOKING HABITS			
	NON	1 - 19	20 +	TOTAL
40-49	4 7918	21 17492	21 12615	46 38025
50-59	14 7635	46 15640	31 8814	91 32089
60-69	16 6172	31 10381	10 3793	57 20344
70 +	3 172	1 671	2 292	6 1082
TOTAL	37 21895	99 44184	64 25.461	200 91540

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Married non-smoking women aged 40 and above -91,540 from a cohort of 265,118 adults in Japan- were asked whether they were smokers, and their husbands were also asked about their smoking habits. The women were followed for 15 years and their death certificates were collected. 200 women died of lung cancer. The table shows the numbers in the age groups according to the smoking habits of the husband. There are only six lung cancer cases in the highest age group, in which the majority of lung cancer cases occur in the population. From these numbers relative risks were calculated. The point estimate of the risk ratio in the group of the women married to men smoking more than twenty cigarettes per day was 1.56 to 1.79, depending on the way of standardization. There was a dose-response relationship which was also significant.

Why is this particular study not conclusive?

The study was not designed to test this hypothesis, but to screen for a wide variety of possible risk factors. It therefore cannot prove the hypothesis. The cohort was not representative of the population. There was an age selection bias. The indicator by which the exposure was measured -being married to a man who smokes- was neither reliable nor valid, nor specific. Also the endpoint was not assessed with validity. We know from experience that lung cancer diagnosis on the death certificate might be erroneous. Confounding factors were not adequately considered, for instance working place, air pollution or medical care. Bias in registering the fact that a woman was a non-smoker was neither controlled nor excluded. Differential misclassification is likely, since in 1965 smoking women were very rare in Japan. Almost nothing is known on the 200 cases. Case reports are missing; autopsy and histology are available in only 11.5%.

Each of these arguments alone could invalidate the results. HIRAYAMA at a recent conference refused to give his material to other researchers for a re-analysis. The core of evidence in the HIRAYAMA study is that during 1965, 200 women in Japan told an interviewer on a single occasion that they were non-smokers, and their husbands said that they were smokers -which could have been different before and thereafter- and their death certificates subsequently contained the -perhaps erroneous- diagnosis of lung cancer. This information is not a convincing scientific data base. I published these and other arguments in 1987 (11).

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TABLE 2: DIFERENCES IN AGE DISTRIBUTION

AGE	PERCENT FEMALE POPULATION	PERCENT HIRAYAMA COHORT
40 - 49	42	42
50 - 59	32	35
60 - 69	20	22
70 +	6 *	1
	100	100

* In the female population 1965 in Japan over 40 there are 12 percent over 70 years old. We assumed here half ot them were still married with a living husband.

Recently we re-analysed the HIRAYAMA data (1) as far as they were published. Table 2 shows the differences in the age distribution between the female population in Japan in 1965 and the HIRAYAMA cohort. Only 1% in the cohort are older than 70 years in comparison to 12% in the population. We reduced this 12% to half -6%- assuming half the women were still married to a living man. It is obvious that there is a strong selection bias by age. When one removes this selection bias -I cannot go into details of calculation here- the relative risks become smaller and are no longer significant.

The first line of Table 3 shows the relative risk as calculated by HIRAYAMA, standardized by age of women only. In the 20+ group it is 1.56 and just significant at the one-tailed 5% level. Correcting for age selection bias the relative risks are much smaller and no longer significant. Considering subgroups -for instance women married to farmers and industry workers- only in the group of industry workers a high relative risk is present

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TABLE 3: RELATIVE RISK IN THE HIRAYAMA STUDY

	HUSBANDS SMOKING HABITS		
	NON	1-19	20 +
RR HIRAYAMA*	**1.00**	**1.37**	**1.56**
IL_{90}		1.00	1.11
RR CORRECTED**	**1.00**	**1.03**	**1.29**
IL_{90}		.77	.94

* Standardized by age of women only
** Age selection bias removed, standardized by age of women
The corrected relative risks are small and no longer significant

after removing the age selection bias. This can be explained by the fact that women married to industry workers might be exposed also to other risks. If one leaves the women married to industry workers out, the relative risk is no longer different from unity. It also decreases considerably by assuming moderate numbers being differentially misclassified. I think this shows that the relative risk of non-smoking women married to men who smoke is not significantly different from unity, provided one considers age selection bias and misclassification. We have published this (1), but other epidemiologists do not share our view.

Another large prospective study from GARFINKEL in the US could not show a risk increase. I carefully evaluated the available studies last year

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and published the evidence with a critical view (11). I cannot describe the 10 case-control studies here in detail. They all have much weaker evidence compared to the HIRAYAMA study.

Nowadays, so-called meta-analysis are used to summarize the evidence from various studies in a formal way. This is useful when studies are similar, especially with controlled clinical trials. However, false plus false does not equal right. Meta-analysis are only valid when the studies included have some minimal quality. The discussion on meta-analysis in this field was started by a paper by WALD et al. (12) two years ago, in which 12 studies are summarized to a significant relative risk of 1.35. The report of the National Research Council and of the Surgeon General in the US followed this publication, the authors being partly the same. Also, the German Research Foundation could not refrain from adding incomparable studies to a single point estimate of risk.

We did our own meta-analysis of the same studies (8). As you can see from Table 4 we grouped the studies according to quality - whether histology was present, whether the exposure measure was somehow critically judged - and we gave a grade from 2 - 6 for overall methodological quality to every study. The study of TRICHOPOULOS got a grade 6 -the worst rating-, the study of GARFINKEL a 2 -our best rating. In the last column we decided for case control studies, whether a single study was of quality+ or of quality- according to these criteria.

In table 5 you see some of our results. The HIRAYAMA study was included with the relative risk corrected for age selection bias. We included women only, since men inflate only the denominator. We also left out the previous smokers in the studies of TRICHOPOULOS and KOO. All resulting relative risks are not different from unity, with the exception when one considers only the 4 case control studies of lower quality. Considering all 12 studies, the relative risk is 1.12. Leaving TRICHOPOULOS out gives 1.08. This study is a textbook example of how a case-control study should not be conducted and analysed. Introducing some cautious assumptions on misclassification, the numbers are still smaller. Also LEE (6) has remarked in his papers that at least part of the evidence can easily be explained by differential misclassification. One can look at the possible meta-analysis in a different way. With 10 case-control studies there are 1023 possible combinations

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TABLE 4: QUALITY RATING OF STUDIES SELECTED FOR META-ANALYSIS

Author	Histology	Exposure	Quality Rating*	Resulting Group
HIRAYAMA	–	–	3	Cohort
GARFINKEL	–	–	2	Cohort
CHAN et al.	+	+	4	CC Quality +
CORREA et al.	–	–	5	CC Quality –
TRICHOPOULOS et al.	–	–	6	CC Quality –
BUFFLER et al.	+	–	4	CC Quality +
KABAT et al.	+	+	4	CC Quality +
GARFINKEL et al.	+	+	4	CC Quality +
AKIBA et al.	–	–	5	CC Quality –
LEE et al.	–	+	5	CC Quality –
KOO et al.	+	+	4	CC Quality +
PERSHAGEN et al.	+	+	4	CC Quality +

* 2 = acceptable, 3 = possibly flawed, 4 = bias and confounding suspected, 5 = major bias and confounding suspected, 6 = unacceptable.

The included studies are the same as in the paper by WALD et al. (1986) and by LETZEL and UBERLA (1988). We included women only.

for meta-analysis. Only 24 of them -2.3%- are technically significant. They are dominated by three studies of low quality, mainly by the TRICHOPOULOS study. All this shows that meta-analysis are very sensitive to the included data, that such sensitivity analysis give some insight into the combination of studies and that they presently do not contribute to our overall evidence regarding passive smoking and lung cancer.

Whether passive smoking causes lung cancer is an open question today. It is therefore not scientifically sound to calculate the attributable risk, i.e. the possible number of deaths attributed to passive smoking per year. All serious scientists refrain from such calculations. Of course, it cannot be ex-

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TABLE 5: SUMMARY OF META - ANALYSIS

HIRAYAMA STUDY CORRECTED FOR AGE SELECTION BIAS CAUTIOUS ASSUMPTIONS FOR MISCLASSIFICATION		
	ORIGINAL DATA	MISCLASSIFICATION ASSUMPTIONS
	RR	RR
ALL 12 STUDIES	1.12	1.04
11 STUDIES (WITHOUT TRICHOPOULOS)	1.08	.99
2 COHORT STUDIES AND 6 CASE CONTROL STUDIES QUALITY +	1.04	.97
6 CASE CONTROL STUDIES QUALITY +	1.07	.90
4 CASE CONTROL STUDIES QUALITY	1.67	1.43

All relative risks are not significant with the exception of meta-analysis for 4 case control studies of quality –

cluded that there is a causal relationship. If there is an effect, it is likely to be very small compared to other risks.

The majority of criteria for a causal connection are not fullfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not

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adequately excluded, there is no intervention study, significance is only present under special conditions and the biologic plausibility can be judged controversially.

There is room for honest differences in opinion. The jury is still out. All epidemiologic evidence can be explained by bias, confounding, misclassification and chance, nearly in the same way as by accepting the alternative hypothesis. Overall, according to the levels of the IARC, there is only inadequate evidence.

Whether passive smoking causes lung cancer is a serious hypothesis. The majority of publications in the field is a little in favor of this hypothesis. However, as I have said, I personally prefer to stay with the null hypothesis for the time being, following my careful analysis of the available evidence.

What can we learn from such a case study in low risk association? Toxicological studies alone cannot provide evidence on the size of a risk to man from indoor air pollution. There is not a single animal study with ETS which succeeded in producing lung cancer. Epidemiologic studies are the way to ascertain whether there is a risk in man, and what the size of the risk is. There are thresholds for human perception and knowledge in epidemiology: relative risks smaller than 2 and incidences smaller than 10^{-5} to 10^{-6} are such thresholds. The concept of a missing threshold for carcinogens should be replaced by more sophisticated models, when one tries to assess the cancer risk of indoor air quality.

REFERENCES

1. ALHBORN, W., UBERLA, K. (1988): Passive smoking and lung cancer: Re-analysis of Hirayama's data. In: Indoor and Ambient Air Quality. R. Perry and P.W Kirk (eds) London, pp.169-178

2. HIRAYAMA, T. (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer : a study from Japan. Br. Med. J 282: 183-185

3. HIRAYAMA, T. (1983) Passive smoking and lung cancer. Consistency of association. Lancet (1): 1425-1426

2023381509

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

4. HIRAYAMA, T. (1984) Lung cancer in Japan: effects of nutrition and passive smoking. IN: Mizell, M., Correa, P. (eds) Lung cancer: causes and prevention. Verlag Chemie, Weinheim, pp 175- 195

5. IARC WORKING GROUP (1985) IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans, vol 36, Lyon, pp 18-19.

6. LEE, P.N. (1988) Misclassification of smoking habits and passive smoking. Springer-Verlag.

7. LETZEL, H. (1988) Passivrauchen und Lungenkrebs. Springer 1988, Reihe Med. Informatik und Statistic, Bd. 69, pp 144

8. LETZEL, H. , BLUMNER, E., UBERLA, K. (1988) Meta-analysis on passive smoking and lung cancer: Effects of study selection and Misclassification of Exposure. In: Indoor and Ambient Air Quality. R. Perry and P. W. Kirk (eds) London, pp. 293-302

9. NATIONAL RESEARCH COUNCIL (1986) Environmental tobacco smoke: Measuring Exposures and Assessing Health Effects. National Academy Press, Washington 1986

10. U.S. Department of Health and Human Services (1986) The Health Consequences of Involuntary Smoking: A Report of the Surgeon General. U.S. DHAS: Washington, D.C.

11. UBERLA, K. (1987) Lung cancer from passive smoking: hypothesis or convincing evidence. Int Arch Occup Environ Health 59, pp 421-437

12. WALD, N.J. et al (1986) Does Breathing Other People's Tobacco Smoke Cause Lung Cancer. British Medical Journal 293, pp 1217-1222.

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15. Johnson LC, Letzel HW (1984) Measuring passive smoking: methods, problems, and perspectives. Prev Med 13:705–716
16. Koo LC, Ho JH-C, Saw D (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J Exp Clin Cancer Res 3:277–283
17. Lee PN, Chamberlain J, Alderson MR (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 54:97–105
18. Lehnert G (Chairman), Garfinkel L, Hirayama T, Schmahl D, Überla K, Wynder EL, Lee P (1984) Roundtable discussion. Prev Med 13:730–746
19. Lubin JH, Blot WJ (1984) Assessment of lung cancer risk factors by histologic category. JNCI 73:383–389
20. MacLennan R, Da Costa J, Day NE, Law CH, Ng YK Shanmugaratnam K (1977) Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. Int J Cancer 20:854–860
21. Muramatsu M, Umemura S, Fukui J, Arai T, Kira S (1987) Estimation of personal exposure to ambient nicotine in daily environment. Int Arch Occup Environ Health 59:545–550
22. National Research Council, Committee on Passive Smoking, Board on Environmental Studies (1986) Environmental tobacco smoke. Measuring exposures and assessing health effects. National Academy Press, Washington, DC, pp 224–227
23. Pershagen G, Hrubec Z, Svensson C (1987) Passive smoking and lung cancer in Swedish women. Am J Epid 125:17–24
24. Rosner B (1982) Fundamentals of Biostatistics. Duxbury Press, Boston, MA, p 176
25. Sellers TA, Ooi WL, Elston RC, Chen VW, Bailey-Wilson JE, Rothschild H (1987) Increased familial risk for non-lung cancer among relatives of lung cancer patients. Am J Epid 126:237–246
26. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B (1981) Lung cancer and passive smoking. Intl J Cancer 27:1–4
27. U.S. Department of Health and Human Services, Public Health Service (1982) The Health Consequences of Smoking: Cancer: a report of the Surgeon General. DHHS Publication No. (PHS)82-50179, p 243
28. U.S. Department of Health and Human Services. Public Health Service (1986) The health consequences of involuntary smoking. Report of the Surgeon General. DHHS Publication No. (CDC) 87-8398, pp 66–102
29. U.S. Department of Health, Education, and Welfare, Public Health Service (1964) Report of the Advisory Committee to the Surgeon General of the Public Health Service. Smoking and health. PHS Publication No. 1103, pp 174–175
30. Wu AH, Henderson BE, Pike MC, Yu MC (1985) Smoking and other risk factors for lung cancer in women. JNCI 74:747–751

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Passive Smoking and Lung Cancer: A Reanalysis of Hirayama's Data

K. Überla and W. Ahlborn

The statistical association between environmental tobacco smoke and lung cancer is controversial. The Hirayama Study seems to provide sound epidemiological evidence supporting this hypothesis. In a recent paper [6] I have analyzed the published studies. Regarding the Hirayama study the following facts have to be kept in mind:

- The study was not designed to test the hypothesis, whether passive smoking is associated with lung cancer or not. It can therefore only generate this hypothesis, not prove it.
- The cohort was not representative for the population of Japan. A selection bias is possible.
- The exposure indicator – the fact of being married to a man who smokes – is not reliable, not valid and not specific.
- The event indicator – dying on lung cancer as noted on death certificates – is neither reliable nor valid.
- Various confounding factors – for instance exposure at the working place, indoor air pollution, overall air pollution, type of medical care – were not accounted for.
- Bias in registering the fact, that a woman is a nonsmoker, was not controlled. Resulting differential misclassifications of the cases, who were smokers and had to be excluded, have not been considered.
- Almost nothing is known about the 200 cases. No case reports are available, autopsy and histology are available in only 11.5%.

The core of the information, on which the results of this study rely, is

1) that during 1965 200 women in Japan told an interviewer on a single occasion that they were – during that time – nonsmokers and their husbands told that they were smokers, which might have been different before and afterwards and
2) that their death certificates subsequently contained the diagnosis lung cancer, which might have been erroneous.

Such sparse information does not seem to be convincing.

In our paper we consider three questions:

1) What is the relative risk when one removes the selection bias regarding age of women in the Hirayama cohort?
2) What is the relative risk for women married to men with different occupations, when one removes the selection bias regarding age of men?
3) What is the relative risk when additionally some differential misclassification is assumed?

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Material and Methods

We start from Tables 1, 2, and 3 of Hirayama 1984 [4]. These tables contain the most detailed published data. In order to check our program, we reproduced some of the reported relative risk estimates with good accuracy.

There are marked differences between the Hirayama cohort and the female age distribution over 40 in the population of Japan 1965. Women 50–59 are overrepresented, women older than 70 are severely underrepresented. In this age group only a single case from 12 was observed. The investigated cohort certainly has a severe selection bias by age, which needs no statistical test. This is likely due to the fact, that the smoking behaviour was not known in the elderly or that the husbands of older women have died. Since it takes 20 years and more from exposure to lung cancer, older women surely are relevant and should not be excluded. The majority of lung cancer cases occur in older age groups, in Germany more than 67% in women over 65 years.

In order to answer the question what the relative risk is when the age selection bias is removed, we adjusted the data to the age distribution of the female population of Japan.

Table 1. Differences between Hirayama cohort and the female age distribution over 40 in the population of Japan 1965*

Age group	Percent female	
	Japan population	Hirayama cohort
40–49	39	42
50–59	30	35
60–69	19	22
70 +	12	1
	100	100

* Population Census 1965. Statistical survey of economy of Japan; 1967. Ministry of Foreign Affairs of Japan.

Table 2. Smoking habit of husband by age of wife.* Original data

Wives age	Husbands smoking habit							
	Non		1–19		20 +		Total	
40–49	4	7,918	21	17,492	21	12,615	46	38,025
50–59	14	7,635	46	15,640	31	8,814	91	32,089
60–69	16	6,170	31	10,381	10	3,793	57	20,344
70 +	3	172	1	671	2	239	6	1,082
Total	37	*21,895*	99	*44,184*	64	*25,461*	200	*91,540*

* Table 2 of Hirayama 1984.

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Table 3. Smoking habit of husband by age of wife*. Removed selection bias: Data adjusted to the age distribution of women in the population

Wives age	Husbands smoking habit							
	Non		1–19		20 +		Total	
40–49	3.91	7,748.8	19.12	15,927.8	20.02	12,024.0	43.05	35,700.6
50–59	12.49	6,813.7	38.20	12,987.1	26.95	7,661.2	77.64	27,462.0
60–69	14.25	5,496.6	25.70	8,604.9	8.68	3,291.1	48.63	17,392.6
70 +	32.02	1,835.9	9.93	6,664.2	20.79	2,484.7	62.74	10,984.8
Total	62.67	*21,895*	92.95	*44,184*	76.44	*25,461*	232.06	*91,540*

* Table 2 of Hirayama 1984.

The technique of iterative proportional fitting of a contingency table to given marginals as described by Bishop et al. [1] or by Hartung et al. [3] was used. This technique keeps the risks constant as observed in every cell and changes the marginals and the cell counts according to the given age distribution of the population. Iterative proportional fitting of contingency tables to given marginals is a well known technique in multivariate statistics and can be applied here without changing the observed interrelations between smoking habit, occupation, and lung cancer. From the fitted or adjusted tables the risk ratios are calculated in the usual way. Such risk ratios based on data with removed age selection bias are the correct ones and should be used.

One has to require that there should be no selection bias by age and the cases should be included as they would have occured in the population. Otherwise statistical tests and p-values are not very meaningful.

Table 2 shows the original data by age of wife. The cells contain the number of lung cancer cases and those under risk as published by Hirayama. The 1–19 group includes ex-smokers in this and the following tables. 200 cases out of 91,540 women were observed. Iterative proportional fitting to the female age distribution of the population leaves the hatched numbers constant. The others are adjusted using a right hand marginal which is made proportional to the age distribution of the population.

Results

Table 3 gives the results of iterative proportional fitting to the female age distribution of the population. It contains the numbers of those under risk and of lung cancer deaths as they would have been observed, if Hirayama had not excluded or preferred certain age groups. The age selection bias is removed. The risks in the individual cells are still the same as those observed by Hirayama. Also the structure of the common distribution regarding age, smoking habit and lung cancer is unchanged. Hirayama would have totally observed 232 cases instead of 200, with the corresponding numbers in the individual cells, had he included all women as they live in the population. This table is the best available starting point for age-standardized risk ratio calculations. It was not used so far.

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Table 4. Relative risk by age of women*

	Husbands smoking habit		
	Non	1–19	20 +
$\widehat{RR}$	1.00	*1.37*	*1.56*
IL_{90}		1.00	1.11
MH-CHI		1.51	2.27
$P_{one\ tailed}$		0.065	0.012**
$\widehat{RR}$	1.00	*0.77*	*1.06*
IL_{90}		0.59	0.80
MH-CHI		2.19	0.27
$P_{one\ tailed}$		0.014***	0.395

Upper part: standardized by age of women only.
Lower part: age selection bias removed and standardized by age of women.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 2 of Hirayama 1984.
** "Significant" in positive direction.
*** "Significant" in negative direction.

In the upper part of Table 4 you find the risk ratios standardized by age only, as done by Hirayama. The lower part are the risk ratios after removing the age selection bias. In the upper part the weighted point estimate of the rate ratio is 1.56 in the 20+-group and is technically "significant". IL_{90} designates the lower point of the 90-percent confidence interval in this and the following tables, as it was used by Hirayama.

This risk increase disappears completely when one removes the selection bias by age. In the 20+-group the rate ratio is 1.06, hardly a relevant risk increase. In the group of 1–19 cigarettes per day it is 0.77 which is a technically significant risk decrease. The adjusted rate ratio, considering all those exposed in one group versus those not exposed is 0.901 with a confidence interval including unity. If Hirayama had observed the cases as they occur in the female population without selection bias by age, he would have observed no risk increase, but a risk decrease. This is the main result of our reanalysis, which corresponds well with the result of the prospective American cohort study as published by Garfinkel [2].

We now consider two occupations, farmers and industry workers. From the upper part of Table 5 one can see that the relative risk for wives of farmers seems substantial, when one standardizes by age of men only. The point estimates of the rate ratios are 1.48 and 1.63 respectively. This was observed earlier and had no adequate explanation. If one removes the selection bias by age and adjusts to the male age distribution of Japan – the numbers in the lower part of Table 5 – the rate ratios are 0.85 and 0.82, not different from unity. This seems more plausible.

Considering the wives of industry workers only, in the upper part of Table 6, the point estimates of the rate ratios are 1.77 and 2.27, standardized by age of men, being not significant. Removing the age selection bias – in the lower part of Table 6 – there is a remarkable risk increase to 4.60 and 6.90, which is significant. However, there are only

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Table 5. Relative risk: wives of farmers only*

	Husbands smoking habit		
	Non	1–19	20 +
$\widehat{RR}$	1.00	*1.48*	*1.63*
IL_{90}		0.97	1.01
MH-CHI		1.48	1.92
$P_{one\ tailed}$		0.069	0.027
$\widehat{RR}$	1.00	*0.85*	*0.82*
IL_{90}		0.59	0.53
MH-CHI		0.42	0.53
$P_{one\ tailed}$		0.337	0.296

Upper part: standardized by age of men only.
Lower part: age selection bias removed and standardized by age of men.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 3 of Hirayama 1984.

Table 6. Relative risk: wives of industry workers only*

	Husbands smoking habit		
	Non	1–19	20 +
$\widehat{RR}$	1.00	*1.77*	*2.27*
IL_{90}		0.70	0.84
MH-CHI		0.73	0.81
$P_{one\ tailed}$		0.232	0.208
$\widehat{RR}$	1.00	*4.60*	*6.90*
IL_{90}		1.71	2.45
MH-CHI		2.50	2.78
$P_{one\ tailed}$		0.006	0.003

Upper part: standardized by age of men only.
Lower part: age selection bias removed and standardized by age of men.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 3 of Hirayama 1984.

9 lung cancer deaths in the 20+-group and only 3 in women 70 years and older, which are small numbers, but these are numbers observed and used by Hirayama and his risk structure is unchanged. Thus only in the subgroup of women married to industry workers there is a risk increase, in all other occupations there is no risk increase. Omitting industry

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Table 7. Relative risk: assumed differential misclassifications*

Number of cases assumed misclassified and removed from exposed groups		Husbands smoking habit		
		Non	1–19	20 +
n = 10 = 5%	$\widehat{RR}$	1.00	*0.74*	*1.00*
	$P_{one\ tailed}$		0.006	0.469
n = 20 = 10%	$\widehat{RR}$	1.00	*0.70*	*0.93*
	$P_{one\ tailed}$		0.003	0.383
n = 30 = 15%	$\widehat{RR}$	1.00	*0.66*	*0.85*
	$P_{one\ tailed}$		0.001	0.238

Age selection bias removed and standardized by age of women.
$\widehat{RR}$: Weighted point estimate of rate ratio.
* Calculated from Table 2 of Hirayama 1984.

workers, the point estimates of the rate ratios are 0.90 and 0.89, not significantly different from unity. These findings are consistent with the assumption of confounding factors in women married to industry workers, who might be exposed to other environmental hazards. Our calculations show that by removing selection bias by age, one can explain hitherto implausible results.

Active smoking is correlated among married couples. In a society in which female smokers were very rare in 1965, more women married to smokers will declare themselves nonsmokers than the other way round. One has therefore to considerr biased or differential misclassification. There are likely more women with lung cancer, who have been misclassified as nonsmokers and have to be removed from the cohort, than the other way round.

We made some moderate assumptions regarding differential misclassification, as shown in Table 7. In order to examine how sensitive the relative risk is we removed 10, 20, and 30 cases from the exposed groups – corresponding to 5, 10, and 15 percent.

Assuming 30 misclassified cases – 15 percent, a percentage which has been observed in the literature [5] – the rate ratios are 0.66 and 0.85. In the group 1–19 cigarettes per day all the risk estimators are significantly smaller than unity. Our personal opinion is that 10 differential misclassified cases from 200, who have to be omitted, are a fair number. The corresponding weighted point estimates of the rate ratio are 0.74 and 1.00. These risk estimates are as reasonable as other risk estimates calculated from the Hirayama data. They indicate – if anything – a risk decrease, not a risk increase.

Discussion

Reanalyses of data, which have been collected by others are not easy. This is because information is not completely available, because information might be misinterpreted or because one has to take another view in order to come closer to the acceptable truth. Our calculations do not diminish the great value and impact the Hirayama study had on the epidemiology of passive smoking. They show however, that reasonable alternative views

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Table 8. Reanalysis of Hirayama's data: summary of relative risk

		Husbands smoking habit		
		Non	1–19	20 +
Age selection bias removed and age-standardized (women)	$\widehat{RR}$	1.00	*0.77*	*1.06*
	$P_{one\ tailed}$		0.014	0.395
Without industry workers, age selection bias removed and age-standardized (men)	$\widehat{RR}$	1.00	*0.90*	*0.89*
	$P_{one\ tailed}$		0.394	0.179
10 cases assumed misclassified, age selection bias removed and age-standardized (women)	$\widehat{RR}$	1.00	*0.74*	*1.00*
	$P_{one\ tailed}$		0.006	0.469

$\widehat{RR}$: Weighted point estimate of rate ratio.

on the same data are possible, which lead to opposite conclusions. Our findings are in contrast to Hirayama's thesis that – based on his data – there is a substantial statistical association between passive smoking and lung cancer.

As long as there is no other independent and sound epidemiological evidence, it should be left to the individual scientist which analysis of the same data he thinks is more appropriate. We do not hold that our view is the only correct one. We do hold however, that the risk ratios calculated by us, removing age selection bias, are as valid as other risk estimates. To our opinion they are more appropriate, since they go back to the population and not to a selected sample. Even when one would take another marginal, for instance the age distribution of wives still married to living men – which was not available – the effect would be considerable. Our risk estimates are a consequence of the data published by Hirayama and cannot be rejected from the study data, as they are published so far.

To summarize (Table 8): Removing the age selection bias in the Hirayama study one gets a relative risk of 1.06 in the group of women married to men with more than 20 cigarettes per day. In the group of women married to men with 1–19 cigarettes per day the relative risk is 0.77, a technically "significant" risk decrease. If Hirayama could have observed the lung cancer cases as they occur in the female population, he would have observed no risk increase, but a risk decrease to around 0.90, considering those exposed versus those not exposed. This fact deserves attention.

If one omits the wives married to industry workers because of possible confounding factors in this group, the relative risk is 0.90 and 0.89 respectively. This is of the same size order and smaller than unity. Here we could adjust and standardize by occupation and age of men only, which is not as appropriate as by the age of women.

If one assumes that 10 cases are differentially misclassified and removes them from the exposed groups, the risk estimates are 0.74 and 1.00, respectively. Our findings demonstrate how sensitive the data of this study are and how weak the evidence for a statistical association between passive smoking and lung cancer might be. In view of these and other facts some of which we mentioned in the introduction, the null hypothesis might be true as well and seems to be consistent with the Hirayama data in the same way as the alternative hypothesis.

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Unrepresentativeness

Although it is clear that the combined study population in Table 1 is not fully representative of non-smokers, this does not appear to be a serious issue, since studies have been carried out in the US, UK, Greece, Sweden, Japan and Hong Kong, and Wald et al. (1986) found no evidence of significant heterogeneity of relative risk estimates.

Sample Size

While none of the studies considered in Table 1 concern particularly large numbers of non-smokers with lung cancer, chance can hardly be the total explanation of the association between passive smoking and lung cancer since the overall relative risk estimate quoted by Wald et al. (1986) of 1.35 is quite highly statistically significant, with 95% confidence limits of 1.19–1.54.

Confounding

Not all the studies considered have taken into account the possible confounding effect of factors known or suspected to be related to lung cancer, such as occupation or nutrition. Although it would perhaps be expected that non-smokers married to smokers might to some extent share the tendency of smokers to work in dirtier jobs, standardisation for occupation, or indeed any confounding factor, has never been found in practice to explain any material part of the association between lung cancer and passive smoking. It does not seem likely that failure to take confounding factors into account has materially affected the issue.

Inappropriate Choice of Controls

General scientific principles demand that like should be compared with like as far as possible. In a number of studies, there were clear exceptions to this. One example is the study of Trichopoulos et al. (1981, 1984) in which controls came from a different hospital. This may cause bias if patients came from different catchment areas with different smoking characteristics. Another example is the recently reported study of Humble et al. (1987), in which virtually all the interviews with controls were conducted directly while much of the data for cases came from surrogates. While inappropriate choice of controls may have materially biassed a few studies, it does not seem very likely, however, that it is a major explanation for the huge discrepancy.

Inaccuracy of Disease Classification

It is well known that diagnosis of lung cancer is imperfect and studies such as those by Garfinkel et al. (1985) which took pains to check and review all available evidence are to be preferred to those that did not do so. However, random misclassification of diagnosis would be expected to reduce the observed association between lung cancer and passive smoking, not increase it, and differential misclassification of diagnosis does not seem very likely, inasmuch as the doctor making the diagnosis is likely to have been blind to the

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patient's ETS exposure in most cases, and not to have been affected by it even if he was, given most diagnoses were made before the first study on the issue was published in 1981.

Non-reporting Bias

A problem in combining results from various studies to come to an overall assessment of the evidence, by so-called "meta-analysis", is the possibility that the studies being combined are not representative of all those that have been carried out. In particular, overall estimates of relative risk may be biassed upward if a scientist is less likely to submit for publication, or a journal is less likely to publish, studies which show no significant relationship of disease to the factor of interest or a significant trend in the direction opposite to that expected in advance. Convincing evidence of bias resulting from this in the context of randomised controlled trials has recently been collected by Chalmers et al. (1987) and the problem may generally be greater in epidemiological studies. One can easily imagine an investigator running a range of statistical analyses, finding a few significant associations of interest, and then publishing papers on those, ignoring the non-significant relationships. One can also imagine journals not being too keen to given space to a paper on a new null association and one must inevitably wonder whether the reason the first two studies published on passive smoking and lung cancer (Hirayama 1981; Trichopoulos 1981) found a significant association was because first published papers on any association tend to be positive. Indeed, there seems a case for carrying out meta-analysis giving most weight to studies showing no association and least weight to studies published first.

Although it is obviously important to conduct research into the problems of non-reporting bias in epidemiological studies, it is difficult to claim that it is the full explanation of the overall association between passive smoking and lung cancer. The reasons for this view are two-fold. Firstly, the overall association remains significant (though the relative risk estimate reduces to 1.20), even after eliminating the Hirayama and Trichopoulos results. Secondly, the fact that lung cancer and passive smoking has been a very "hot" issue in recent years suggests researchers should now be able to publish results from studies showing no association between passive smoking and lung cancer risk.

Lack of Objective Measure of ETS Exposure

A limitation of all the published epidemiological evidence is lack of objective measurement of exposure to ETS. Subjects are classified mainly by whether or not they are married to a smoker and occasionally by reported degree of exposure outside the home, but there are no data available either on ambient levels of tobacco smoke constituents at home or at work or on levels in body fluids such as blood, urine or saliva. While (e.g. see Table 3) it can be shown that marriage to a smoker is indeed associated with increased levels of cotinine, the relatively crude method used for determining exposure leads to possibilities of bias in case-control studies where knowledge of disease may consciously or subconsciously affect reporting of ETS exposure. While this may have caused upward bias of the reported relative risk in some case-control studies, it can hardly explain the whole association, since it would not be expected to cause upward bias in prospective studies and the association seems as strong in prospective as in case-control studies.

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Table 5. Hypothetical example of bias due to misclassification of 5% of smoking subjects as non-smokers

Smoking habit*		Assumed		Observed			
Subject	Spouse	N	Risk	N	Risk	Passive effect	Active effect
NS	NS	60	1	60 + 2 = 62	1.61	1	
NS	S	40	1	40 + 3 = 43	2.33	1.44	
NS	Total	100	1	100 + 5 = 105	1.90		1
S	NS	40	20	40 − 2 = 38	20		
S	S	60	20	60 − 3 = 57	20		
NS	Total	100	20	100 − 5 = 95	10		10.5

Assumed concordance = (60 × 60)/(40 × 40) = 2.25
Observed concordance = (62 × 57)/(43 × 38) = 2.16

* NS, non-smoker; S, smoker

Lack of Objective Measure of Active Smoking Status

Although considered last, this appears to be the most serious problem affecting the epidemiological evidence on passive smoking and lung cancer. As will be shown in the next section, completely erroneous conclusions can be reached when the "non-smokers" being studied actually include a small proportion of misclassified true smokers.

Misclassification of Active Smoking Habits as a Major Source of Bias

As shown in Table 5, misclassification of a small proportion of smokers as non-smokers, coupled with a tendency for smokers to be married to smokers ("concordance") can create an apparent positive effect of passive smoking when no actual effect exists. It also leads to an underestimation of the active smoking effect and of the concordance. The passive smoking bias depends critically on the assumed relative risk for active smoking, the degree of concordance and on the level of misclassification of subject smokers as non-smokers. This source of bias will also produce an artificial dose response relationship when the "non-smoking" subjects are divided according to the amount smoked by the spouse. It can be shown (Lee 1988b) that misclassification of non-smoking subjects as smokers and of smoking spouses as non-smokers causes a degree of bias that is minor compared with that resulting from misclassification of smoking subjects as non-smokers.

In an attempt to determine the extent to which smokers misreported their smoking habits and to which smokers tend to be married to smokers, Lee (1987) carried out three separate studies. In the first study, which concerned accuracy of reported current habits, 1775 British subjects were asked about their smoking habits and use of other nicotine products in a non-health context likely to minimize underreporting of smoking. They were then (with no prior warning) asked to provide saliva for cotinine analysis and 1537 agreed to do so. As shown in Table 3 there was in general a very marked difference between the cotinine levels of tobacco users and non-users. Using 30 ng/ml as a cut-off,

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1.1% of self-reported non-users could be classified as occasional users, with levels of to 100 ng/ml, while 1.4% could be classified regular users, with levels above 100 ng/ml.

The second study, which aimed at obtaining information, on accuracy of past smoking habits, followed up in 1985 540 subjects previously interviewed in 1980 about their smoking habits. Ten% claiming on one occasion never to have smoked made inconsistent statements on the other occasion, with inconsistent smokers being more often men, old, smokers of fewer cigarettes and long term ex-smokers.

The third study, which aimed at obtaining information on smoking habit concordance, involved 8857 subjects aged 16+ interviewed regarding their own smoking habits and that of their spouse. The concordance ratio, 3.55 in men and 3.07 in women, was found to be rather greater than that assumed in the example in Table 5. Concordance rose with amount smoked. Thus, the chance of having a spouse who was a manufactured cigarette smoker was 22% for subjects who reported no such smoking, and 45%, 52% and 59% respectively for subjects who reported smoking 1–17, 18–22 and 23+ manufactured cigarettes per day.

From the data obtained, Lee (1987) concluded that misclassification could bias relative risk estimates in relation to passive smoking upwards by a factor of 1.31 in men and 1.24 in women, not significantly different from the pooled estimate of risk in relation to passive smoke exposure.

At about the same time as Lee presented his findings, Wald et al. (1986) used similar techniques to estimate the bias from misclassification, but based on a number of smaller, and less representative studies, not specifically designed for the purpose. They estimated this misclassification would have less effect, reducing the pooled estimate of risk only from 1.35 to 1.30, i.e. it had only caused upward bias by a factor of 1.04.

Examination of the detail of how the estimates of bias of Wald et al (1986) and of Lee (1987) were arrived at reveals three reasons for the difference. The first was that Wald et al. (1986) used an assumed relative risk of 8 for the effect of active smoking observed in women whereas Lee (1987) used 10. The second was that the calculations of bias by Wald et al. (1986) were mathematically inaccurate, due to confusion between true relative risks in relation to active smoking and those observed (which are affected by misclassification). These are less important than the third reason, which is that Lee et al. (1987) found that 1.4% (10/808) self-reported non-smokers were current regular smokers, whereas Wald et al. (1986) only found 0.14% (1/705) such cases.

In an attempt to reconcile this difference, I have recently conducted a detailed literature review of the evidence on misclassification of smoking habits, which will be published as a book early in 1988.

Despite the various study designs and populations involved a number of clear conclusions were reached:

(1) Even in circumstances that are apparently similar quite a wide variation in the extent of misclassification can be found.
(2) The proportion of "non-smokers" subsequently found actually to be smokers is markedly higher in smoking cessation studies than in studies where the respondent is under no special pressure not to smoke.
(3) The proportion of "non-smokers" subsequently found actually to be smokers is also markedly higher in lung cancer patients than in the general population. This is not surprising in view of the overall *a priori* expectation that a lung cancer patient actually is a smoker.
(4) Studies of "non-smokers" without lung cancer and under no special pressure not to smoke suggest that around 4% are likely actually to be current smokers. While not all

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studies provide information on the extent to which such misclassified smokers smoke, and those that do indicate many of them are occasional smokers, it seems that 1 to 2% of self-reported non-smokers are regular smokers.

(5) In addition to these misclassified current smokers there are a somewhat larger number of ex-smokers misclassified as never smokers. Available information suggests that these tend to have smoked less and a longer time ago than average ex-smokers.

(6) None of the studies have investigated whether the extent to which smokers deny smoking depends on whether their spouse happens to smoke, which is of theoretical importance as it could materially affect estimates of bias.

(7) There is even now virtually no information on the extent to which smoking habits might be misclassified in Japan and Greece, from whence came the early epidemiological evidence on passive smoking and lung cancer. The only study in Japan, by Akiba et al. (1986), provided data suggestive of substantial misclassification of smoking habits. Here, of 187 men who reported not smoking in 1964–68, as many as 96 (51%) reported in 1982 that they had smoked.

While there is an obvious need for further research on misclassification of smoking habits the results of the review[1] suggested strongly that Wald et al. (1986) had seriously underestimated its importance.

Overall Conclusion

It has clearly been shown that there is a huge discrepancy between the relative doses of smoke constituents to which passive and active smokers are exposed and the much larger relative effect claimed from epidemiological evidence. The most likely explanation for this discrepancy seems to be a persistent bias affecting all the studies due to a small proportion of smokers being wrongly classified as non-smokers in the epidemiological studies.

References

Adlkofer F, Scherer G, von Hees U (1985) Passive smoking. N Engl J Med 312:719–720

Akiba S, Kato H, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Research 46:4804–4807

Alderson MR (1983) An introduction to epidemiology. Macmillan

Alderson MR, Lee PN, Wang R (1985) Risks of lung cancer, chronic bronchitis, ischaemic heart disease and stroke in relation to type of cigarette smoked. J Epidemiology and Community Health 39:286–293

Arundel A, Irwin T, Sterling TK, Weinkam J (1986) Nonsmoker lung cancer risks from exposure to tobacco smoke particulates. Stated to be available on request in: Arundel A, Irwin T, Sterling T. Nonsmoker lung cancer risks from tobacco smoke exposure: An evaluation of repace and lowrey's phenomenological model. J Environmental Science and Health Part C 4:93–118

Buffler PA, Pickle LW, Mason TJ, Contant C (1984) The causes of lung cancer in Texas. In: Lung cancer causes and prevention. Chemie International Inc, pp 83–99

[1] Supported by a recent large study by Coultas et al. (American Review of Respiratory Diseases, 1987, 136, 305–309) who found 63 subjects with salivary cotinine >20 ng/ml among a sample of 1,360 New Mexicans reporting they were not current smokers.

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Chalmers TC, Levin H, Sachs HS, Reitman D, Berrier J, Nagalingam R (1987) Meta-analysis of clinical trials as a scientific discipline. I: Control of bias and comparison with large co-operative trials. Statistics in Medicine 6:315–325

Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. Cancer campaign. In: Cancer epidemiology. Fischer, vol 6, 199–202

Correa P, Pickle LW, Fontham E, Lin Y, Haenszel W (1983) Passive smoking and lung cancer. Lancet 2:595–597

Dalager NA, Pickle LW, Mason TJ, et al (1986) Relation of passive smoking to lung cancer. Cancer Research 46:4808–4811

Doll R (1986) Lung cancer observed and expected changes in incidence from active and passive smoking. XIV UICC Conference, Budapest

Doll R, Peto R (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiology and Community Health 32:303–313

Garfinkel L (1981) Time trends in lung cancer mortality among non-smokers and a note on passive smoking. J National Cancer Institute 66:1061–1066

Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: A case-control study. J National Cancer Institute 75:463–469

Gillis CR, Hole DJ, Hawthorne V, Boyle P (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Resp Dis [Suppl 133] 65:121–126

Hiller FC, Mazumder MK, Wilson JD, McLeod PC, Bone RC (1982a) Human respiratory tract deposition using multimodal aerosols. J Aerosol Science 13:337–343

Hiller FC, McCusker KT, Mazumder MK, Wilson JD, Bone RC (1982b) Deposition of sidestream cigarette smoke in the human respiratory tract. American Review of Respiratory Diseases 125:406–408

Hirayama T (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 282:183–185

Hirayama T (1984) Cancer mortality in non-smoking women with smoking husbands in a large-scale cohort study in Japan. Preventive Medicine 13:680–690

Humble CG, Samet JM, Pathak DR (1987) Marriage to a smoker and lung cancer risk. Am J Public Health 77:598–602

Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Salloojee Y (1984) Biochemical markers of smoke absorption and self-reported exposure to passive smoking. J Epidemiology and Community Health 38:335–339

Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221

Koo LC, Ho JH-C, Saw D (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J Experimental and Clinical Cancer Research 3:277–283

Koo LC, Ho JH-C, Saw D, Ho C-Y (1987) Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. Int J Cancer 39:162–169

Lee PN (1984) Passive smoking. In: Cumming G, Bonsignore G (eds) Smoking and the lung. Plenum Publishing Corporation, p 216

Lee PN (1987) Passive smoking and lung cancer association: A result of bias? Human Toxicology 6

Lee PN (1988a) Difficulties in studying weak associations epidemiologically with particular reference to environmental tobacco smoke exposure and lung cancer (submitted for publication)

Lee PN (1988b) Passive smoking and lung cancer. Association on artefact due to misclassification of smoking habits. Springer (in press)

Lee PN, Chamberlain J, Alderson MR (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 54:97–105

Matsukura S, Taminato T, Kitano Y, et al (1984) Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers. N Engl J Med 311:828–832

Pershagen T, Hrubec Z, Svensson C (1987) Passive smoking and lung cancer in Swedish women. Am J Epidemiology 125:17–24

Pittenger DJ (1985) Passive smoking. N Engl J Med 312:720

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Robins J (1986) Risk assessments – exposure to environmental tobacco smoke and lung cancer. Appendix D to environmental tobacco smoke. Measuring exposure and assessing health effects. Committee on passive smoking. Board on environmental studies and toxicology, pp 294–336, Washington, DC. National Research Council. National Academy Press

Trichopoulos D, Kalandidi A, Sparros L, Macmahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1–4

Trichopoulos D, Kalandidi A, Sparros L (1983) Lung cancer and passive smoking: Conclusion of Greek study. Lancet 2:677–678

Wald NJ, Nanchahal K, Thompson SG, Cuckle HS (1986) Does breathing other people's tobacco smoke cause lung cancer? Br Med J 293:1217–1222

Wells AJ (1986) Misclassification as a factor in passive smoking risk. Lancet 2:638

Wu AH, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. J National Cancer Institute 74:747–751

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An Introduction to the Study of Smoking Using Urinary Hydroxyproline

H. Kasuga

Summary

The indicators used to identify the effects of environmental tobacco smoke (ETS) and exposure to low level nitrogen dioxide (NO_2) on the respiratory system are so weak that they can not be detected using traditional markers such as the increased prevalence of respiratory symptoms and a decrease in lung function. After studying urinary hydroxyproline (HOP) starting in 1977, we first reported the significant relationship between HOP and smoking, ETS and NO_2 in the air, in 1981. Since then, the coherent association between urinary HOP and the established pathological and biological development of lung diseases has been studied. Bias problems based on confounding factors, misclassification of nonsmokers and over- or underestimation of ETS effects also have been discussed.

Among articles presented by us during the past 4 years, several papers and some arguments for and against this study on urinary HOP were introduced:

1) The effect of cessation from smoking on the urinary excretion of hydroxyproline [19].
2) A prospective repeated cross-sectional study on the possible health effects caused by automobile exhaust and passive smoking [20].
3) Impact of smoking on the concentration and activity of alpha-1-antitripsin in serum, in relation to the urinary excretion of hydroxyproline. Matsuki H, Kasuga H et al., 1988.
4) Behavior of urinary hydroxyproline and effect of cigarette smoking in silicosis. Osaka F, Kasuga H, Matsuki H et al., 1985.
5) Opinions contrary to the relationship between urinary hydroxyproline and smoking, ETS and NO_2.

Introduction

Hydroxyproline (HOP) is one of the essential constituents in collagen and elastine and is an unique one which is not found in other tissues. Therefore, urinary HOP is regarded to be a potential candidate for the study of the breakdown of lung tissue due to smoking and environmental tobacco smoke (ETS).

As is generally known, the index symptom such as "a persistent cough and phlegm" based on the BMRC Questionnaire [1] is used frequently as a clinical marker, but it is not applicable for ETS effects because prevailing concentrations of ETS are estimated to be less than 1% of an undiluted mixture of sidestream and second-hand mainstream smoke. Therefore, urinary HOP as a biochemical marker for ETS effects appeared on the stage, and a causal relationship between smoking including ETS and its health effect was

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We would be glad to apply our technique to more detailed data if we can get them from Hirayama, for instance in order to adjust by occupation of men and age of women, or by occupation of men and by age of women married to a husband who is still alive. We are ready to modify our view if such data can support the alternative hypothesis better than the published data. We do hope, that our calculations give rise to a fruitful discussion. The methods we used here might be of interest to the analysis of other cohort and case control studies.

References

1. Bishop YV, Fienberg StE, Holland PW (1980) Discrete multivariate analysis: theory and practice. MIT Press, Cambridge, pp 97
2. Garfinkel L (1984) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J Natl Canc Inst (USA) 66:1061–1066
3. Hartung J, Elpelt B, Klösener KH (1985) Statistik. Lehr- und Handbuch der angewandten Statistik. München Wien Oldenburg, p 501–503
4. Hirayama T (1984) Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Chemie, Weinheim, pp 175–195
5. Lee PN, Chamberlain J, Alderson HR (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer (54):97–105
6. Überla K (1987) Lung cancer from passive smoking: hypothesis or convincing evidence? Int Arch Occup Environ Health (59):421–431

2023381520

What Is the Epidemiologic Evidence for a Passive Smoking-Lung Cancer Association?

N. Mantel

Summary

Two survey articles of reports on the association of passive smoking with lung cancer have recently appeared, and also a comprehensive report on the subject of environmental tobacco smoke by a committee of the National Research Council of the United States. The observed excess over a relative risk of unity cannot be explained by chance. Nor can it be fully accounted for by a particular source of bias, the false claims of being non-smokers by individuals who were active or ex-smokers. That possible source of bias leads, in one summary survey, to reducing a relative risk of 1.35 to 1.30, but from 1.34 to 1.15 in the National Research Council report. The latter report suggests that statistical significance would no longer obtain, perhaps, particularly, because of other possible biases. However, to get an estimate of the correct relative risk due to passive smoking, allowance has to be made for actual exposure to passive smoking of those not exposed at home. Thus, the 1.30 is adjusted upwards, by 18 in one survey, to 1.53, but by only 8% in the National Research Council report to 1.24. The National Research Council report had given an anticipated relative risk of 1.1 based on dosimetric considerations. But it is suggested here that that could be as low as 1.05, too low to be detected in an epidemiologic investigation – in any case it would be based on hypothetical assumptions.

In November of 1986 there were two near-simultaneous review articles addressing the subject of passive smoking and lung cancer. One was an invited guest editorial by Blot and Fraumeni in the Journal of the National Cancer Institute, the other a contemporary theme discussion by Wald et al. in the British Medical Journal [1, 2].

There was substantial overlapping in the two articles of the various publications on the subject, and on the basis of which the conclusion of a significant positive association was made. The article by Wald et al. gave, perhaps, more statistical detail about the results of the several studies covered. But, to my mind, there was uncritical acceptance of the results of all the studies. Blot and Fraumeni did suggest that there were some flaws in a particular study, that by Hirayama [3], but decided that any inherent biases in that investigation could not have given rise to the observed elevated risk.

From their overall evaluation of 10 case-control studies (all 10 gave results for females, five separately for males as well) and three prospective studies (two of these covered males separately), which provided 20 separate relative risk (actually odds ratio) values, Wald et al. came up with a summary relative risk of lung cancer due to passive smoking of 1.35 (95% limits 1.19 to 1.54). They trim this down to 1.30 on the basis that some of the presumed non-smokers exposed to passive smoking were actually smokers. Then, on the added basis that even those unexposed to passive smoking at home may still have been exposed when away from home, they raise their estimate of relative risk to 1.53. But note that this last modification presupposes the answer, that passive smoking does

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Anyway, let's have a look at some of the summary data given. Collectively, for wives of non-smokers we have 32 lung cancers among 21 895 women versus 86/44 184 for ex-smokers or light smokers versus 56/25 461 for heavy smokers. That would yield a single df χ^2 by the method Dr Hirayama apparently used of 3·31, or a χ value of 1·82, not significant, two tailed, at the 5% level. Dr Hirayama, however, reports a χ value of 3·30, with a two-tailed probability level beyond 0·1%. The question then is whether he has conducted a more refined analysis, about which he is giving us no clues, or he has mistakenly interpreted his χ^2 value as a χ value.

As an example of a particularly striking association, Dr Hirayama concentrates on the results for non-smoking wives of agricultural workers aged 40-59. The corresponding data for this group are 3/5 999 versus 20/12 753 versus 16/7 150, which would yield a χ^2 of 6·45, a χ value of 2·54. Dr Hirayama reports a surprisingly close χ value of 2·60, with an associated significance level of 0·94%. As an extreme outcome of several possible analyses available to him this is not really all that significant. But if the difference between 2·54 and 2·60 reflects only rounding errors in calculations rather than distinctly different analyses, this would make it more likely that Dr Hirayama's 3·30 value is a χ^2 rather than a χ, which, as such, does not have the extreme statistical significance which he has attached to it.

Much more careful analysis of the data would be needed before it can be claimed that a passive effect of smoking has been clearly established.

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To Dr Takeshi Hirayama

In a recent press release the Tobacco Institute in the United States challenged the statistical validity of your finding that non-smoking wives of heavy smokers have a higher risk of lung cancer. The central point raised by the Tobacco Institute was that you erred fatally in your calculation of a critical test statistic and therefore that your claim of a high level of statistical significance is wrong. The Tobacco Institute's assertions relied heavily on a speculation contained in a memorandum on your study by Dr Nathan Mantel. The purpose of this letter is to inform you of the details of Dr Mantel's analysis, and in particular the origin of the alleged arithmetical error. Your results, at least those published, do indeed display a high level of statistical significance. If there is an error of inference in your study, it is far less superficial than the alleged arithmetical mistake publicised by the Tobacco Institute.

The essential data are given in the attached table, which we derived from tables I and II of your paper in the *B.M.J.* (17 January, p 183). The population of non-smoking wives at the beginning of the prospective study and the number of lung cancer deaths during 14 years of observation are broken down according to the age, occupation, and smoking habits of their husbands. Also provided are the corresponding 14-year lung cancer death rates for each cell. At the bottom of the table the data for all age and occupational categories of husbands are combined.

In his memorandum to the Tobacco Institute, Dr Mantel calculated a χ^2 test statistic with one degree of freedom from the *combined* data, and obtained the result $\chi^2 = 3{\cdot}31$, which would yield a two-sided $p = 0{\cdot}07$. In performing this test he used the scoring 0, 1, 2 for the three smoking categories. This value of χ^2 looked suspiciously close to the value of $\chi = 3{\cdot}299$ reported on page 183 of your paper. On this basis, Dr Mantel *speculated* that you may have failed to take a simple square root in your calculation.

If, however, a χ^2 test statistic with one degree of freedom is calculated from the *disaggregated* data in the table, then the result is $\chi^2 = 8{\cdot}09$, which yields a highly significant two-sided $p = 0{\cdot}004$. In making this calculation we used formulas (2) through (4) on page 694 of Dr Mantel's original paper,[1] which shows how to combine χ^2 statistics from the four independent contingency tables. The reason for the increase in statistical significance is that the dose-response relation between the husband's smoking habit and the non-smoking wife's lung cancer rate, which is apparent from the combined data, becomes even more prominent when the data are broken down by age and occupational categories of the husband. That is exactly what Dr Mantel's extension χ^2 was designed to test.

We reach the same conclusion of a high level of statistical significance when the disaggregated data are fitted to a number of plausible statistical models. For example, if P_{ij} denotes the 14-year lung cancer death rate of a non-smoking woman whose husband belongs to age-occupational category $i = 1, 2, 3, 4$ and smoking category $j = 1, 2, 3$, then the traditional relative risk model $P_{ij} = a_i \cdot r_j$ yields a good statistical fit with an equally strong level of significance. (The 6-degree-of-freedom χ^2 goodness-of-fit statistic is 5·3, with $p = 0{\cdot}5$.) For this model, the estimated relative risk of lung cancer for the intermediate category of smoking husbands is 1·42 (95% confidence interval 0·95 to 2·13) by maximum-likelihood methods. The estimated relative risk of lung cancer for the heavy-smoking husbands is 1·87 (95% confidence interval 1·21 to 2·91). These estimates are consistent with the relative risks reported in your paper.

In fairness and respect to Dr Mantel, we wish to point out that his speculation of an arithmetical error was only a minor point in his memorandum. The greater part of Dr Mantel's criticisms was devoted to ambiguities in your method of presenting the results. Thus it is not entirely clear to us whether you based your statistical calculations on more finely disaggregated age and occupational groups than those reported in the paper and reproduced by us here. It is unclear whether you used the number of person-years at risk or the number of persons at risk in your calculations of statistical significance. It is also not clear to us whether you standardised on the ages of the wives themselves. Such calculations, if not already performed, would certainly make the analysis more conclusive. But we see no obvious reason why these additional analyses should produce substantially different results.

The Tobacco Institute's claim that your study is invalidated by a trivial arithmetical error has become an international news story. We recognise that you, as author of the paper under challenge, are in the most appropriate position to respond publicly. As your colleagues in the scientific community, we urge you to uphold the validity of your paper.

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[1] Mantel N, Haenszel W. *Journal of the American Statistical Association* 1963;58:611-27.

SIR,—The far-reaching implications of the paper on passive smoking (17 January, p 183) make it imperative to determine whether the data on which it is based are adequate for the purpose.

In none of his several reports on this population does Hirayama explain how he selected his study population. There are 46 prefectures in Japan. Within these prefectures there are 832 health stations. In the six prefectures from which the 69 health stations were selected there are 173 health stations. How were the 69 selected? In one report it was stated that they were the medically adequate ones, which would introduce certain biases. The six prefectures included in the study contain most of the heavy industries in Japan and also border the sea. Shipbuilding, for example, in which Japan leads in world production, is associated in the United States with asbestos exposure. Since shipbuilding is a major industry in one of the prefectures in the study, were the health stations selected for the study for residents in the shipbuilding areas? Industry in Japan supplies medical care to workers and their families as one of the perquisites of employment. Were the families covered by industry omitted from the study? If so, the healthiest segment of the population was omitted.

The figure of 91·99%, of the population of the health stations is given to demonstrate the population basis of these data. To what population is Hirayama referring? Is the census in Japan taken of health stations—that is, of individuals eligible for care in health stations? Is not attendance at the health stations the option of the individual? In the *Japanese Almanac* for 1972, the proportion of females visiting the health stations ranges from 2·5% in Miyaga to 14·5% in Osaka. How can this be population based? And if it is population based why were the rates figured by the person-year method rather than on the actual population?

Personal interview surveys usually elicit more complete response than mailed questionnaires or hospital record searches. In this study, on the pivotal question of occupation 44 357 (31·04%)

*Lung cancer deaths in non-smoking Japanese wives during 14 years of observation: data based on tables I and II of Hirayama's paper**

Husband's smoking habit:	Non-smoker	Ex-smoker or 1-19 cigarettes/day	≥20 cigarettes/day
Disaggregated data			
Husband aged 40-59 years and working in agriculture:			
Population of wives at risk	5999	12 753	7150
No of deaths from lung cancer	3	20	16
Lung cancer deaths per 10 000	5·0	15·7	22·4
Husband aged 40-59 years and working elsewhere:			
Population of wives at risk	8021	17 923	13 434
No of deaths from lung cancer	8	20	20
Lung cancer deaths per 10 000	10·0	11·2	14·9
Husband aged 60 years or more and working in agriculture:			
Population of wives at risk	4407	7291	2241
No of deaths from lung cancer	14	32	8
Lung cancer deaths per 10 000	31·8	43·9	35·7
Husband aged 60 years or more and working elsewhere:			
Population of wives at risk	3468	6217	2636
No of deaths from lung cancer	7	14	12
Lung cancer deaths per 10 000	20·2	22·5	45·5
Combined data			
Husbands of all ages and occupations:			
Population of wives at risk	21 895	44 184	25 461
No of deaths from lung cancer	32	86	56
Lung cancer deaths per 10 000	14·6	19·5	22·0

* *BMJ* 1981;282:183-5.

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women surveyed and 6245 (40·19%) of the women smokers were listed as unknown or not specified as to occupation. Was this study part of a larger study collected for a different purpose, a national health survey perhaps? This could explain this large number of unknowns in this important category.

It is unusual to have such a study based on the ages of the the husband at time of interview rather than on age of the study subjects, the wives. When the agricultural and non-agricultural comparisons were made, the experience of the wives of men over 69 was omitted, an important segment of the study population. Why was this? Clarification of these points would be appreciated.

A recent study in Japan by Minowa *et al*[1] considers the distribution of lung cancer mortality and many of the environmental factors in Japan. In this carefully conducted and explained study, the author states, "Smoking did not seem to explain the prefectural differences of lung cancer mortality." There was no significant difference between the prefectures with high and low consumption of tobacco. The high standardised mortality ratios were along the seacoast, in the highly polluted and heavy industry areas for both males and females. The areas in Hirayama's study were nearly all in the areas with the high standardised mortality ratios in the Minowa study. Aoki,[2] another reputable epidemiologist from Japan, reported in 1980 on the incidence of lung cancer and its mechanism as regards factors other than smoking. Before the second world war lung cancer was a rare disease but during 1947–60 the number of deaths increased rapidly. Such an increase cannot be explained by smoking. These authors make the point that Japan has a disproportionate amount of adenocarcinoma, and Hirayama also mentions the large number of adenocarcinomas in the cases from this study that had a postmortem examination. The proportion of adenocarcinomas of the lung in Japan, twice as high as in any of the developed countries in the world and validated by an outstanding Japanese thoracic specialist, Ishikawa,[3] indicates aetiological factors peculiar to Japan, specifically related to adenocarcinoma.

Since histology is critical in determining prognosis, treatment, and aetiology in lung cancer, and adenocarcinoma is a different disease from squamous-cell carcinoma, and is omitted from many studies on results of smoking because the relationship is not established, to attribute causal dependence to the single aetiological factor of passive exposure to tobacco smoke regardless of histology raises serious questions.

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[1] Minowa M, Shigematsu I, Nagai M, Fukumoto K. *Soc Sci Med* 1981;15D(1):225–31.
[2] Aoki K, Ohno Y. *Nippon Rinsho* 1980;38:2541–50.
[3] Ishikawa S. *Jpn J Clin Oncol* 1973;3:19–30.

SIR,—The validity of the significance test used in my paper was kindly confirmed by prominent statisticians in many institutes, including the US National Cancer Institute and the Massachusetts Institute of Technology.

Professor Macdonald apparently misunderstood the method used in our study. A complete interview survey was done for 265 118 adults aged 40 and above at the time of (or in some cases just subsequent to) the national census in 1965 in 29 health centre districts in six prefectures. This was not a random survey but the satisfactory representativeness of the study samples with regard to demographic and social indices was confirmed after the survey. Asbestos exposure is quite unlikely to have influenced our result since the proportion of industrial areas are surely not in excess in our sample. The husbands' ages are closely associated with wives' ages. Since smoking habit is a characteristic of the husbands, the husband's age was used. We have tables by wives' ages separately.

The age-occupation-specific mortality asked for by Mr Kornegay and Dr Kastenbaum is shown in the accompanying table I. The statistical test on the overall results revealed a highly significant association.

Garfinkel's results[1] in the United States, which failed to show a significant dose-response relationship between amount of cigarette smoking by the husbands and the mortality of their non-smoking wives from lung cancer, are not a surprise to me. The discrepancy could be partly due to different methodology. Our study in Japan is based on census population and husbands as well as wives were interviewed with a 95% response rate. Since Garfinkel's series was based on volunteers' interviews, the husband's smoking history was available only for 27·1% of the non-smoking wives with lung cancer, 153 out of 564, in sharp contrast to 72·3% in our series (174 out of 240).

When, however, one compares the three recent studies—those of Garfinkel,[1] Trichopoulos *et al*[2] and ours—the difference between the actual and the expected mortality from lung cancer in non-smoking wives of smoking husbands were all in the same direction (table II); and a sound researcher will conclude that the size of the study samples should be increased, especially in the US series.

Other possible reasons for the different results between the United States and Japan include (*a*) a higher percentage of office workers in females in the United States than in Japan, 31·9%, and 14·6%, respectively in 1975; (*b*) a higher divorce rate in the United States than in Japan, 4·1%, and 1·1% in 1975 respectively, indicating the need for consideration of smoking habits of ex-husbands in the United States; (*c*) smaller room size in Japan; (*d*) absence of the custom of asking, "Do you mind if I smoke?" in Japan; (*e*) other confounding variables.

In the survey conducted in Aichi Prefecture, one of our study areas, the number of passively smoked cigarettes and the length of exposure in the household was measured to estimate the quantity of sidestream smoke inhaled by the wives (table III). The number of cigarettes passively

TABLE I—*Mortality for lung cancer in non-smoking women by age, occupation,* and smoking habit of the husband*

Husband's age	Husband's occupation	Husband's smoking habit: Non-smoker — No of deaths	Non-smoker — Population	Ex-smoker or 1-19 cigarettes/day — No of deaths	Ex-smoker or 1-19 cigarettes/day — Population	≥20 cigarettes/day — No of deaths	≥20 cigarettes/day — Population	χ	Two-tailed p value
40–49	Total	5	6229	12	15034	15	10764	1·367	0·17163
	1	0	324	0	653	0	566		
	2	0	90	0	231	1	293	0·932	0·35134
	3	1	908	1	2247	3	1867	0·650	0·51569
	4	1	476	0	993	0	1044	−1·646	0·09976
	5	1	2502	6	5941	9	3636	2·297	0·02162
	6	0	46	0	185	0	108		
	7	0	177	1	486	1	426	0·541	0·58851
	8	1	1112	3	3431	1	2241	−0·545	0·59575
	9	0	162	1	345	0	243	−0·148	0·88234
	10	1	432	0	542	0	340	−1·217	0·22360
50–59	Total	6	7791	28	15642	21	9820	2·164	0·03046
	1	0	345	0	593	2	446	1·740	0·08186
	2	0	175	0	253	1	319	1·020	0·30773
	3	1	817	4	1764	1	1324	−0·436	0·66284
	4	1	653	2	1133	4	1092	0·955	0·33958
	5	2	3497	14	6812	7	3514	1·455	0·14567
	6	0	35	0	89	0	50		
	7	0	120	0	273	1	234	1·120	0·26271
	8	2	1375	6	3478	2	2155	−0·502	0·61567
	9	0	164	0	378	1	251	1·243	0·21387
	10	0	610	2	869	2	435	1·411	0·10718
60–69	Total	16	7120	42	12643	19	4651	1·790	0·07345
	1	0	227	0	327	1	179	1·434	0·15157
	2	1	91	0	143	0	124	−1·413	0·15766
	3	0	305	2	594	2	327	1·341	0·17992
	4	2	508	5	822	1	500	−0·459	0·64623
	5	11	4084	31	6845	8	2152	0·918	0·35862
	6	0	9	0	31	0	14		
	7	0	45	0	82	0	55		
	8	0	805	3	1784	3	736	1·872	0·06121
	9	1	121	0	208	0	92	−1·311	0·18986
	10	1	925	1	1607	4	472	2·391	0·01680
70 and over	Total	5	755	4	1085	1	226	−0·694	0·48768
	1	0	32	0	30	0	5		
	2	0	21	0	14	0	4		
	3	0	18	1	36	0	8	0·255	0·79872
	4	0	48	0	73	0	20		
	5	3	323	1	444	0	89	−1·494	0·13518
	6	0	1	0	1	0	0		
	7	0	1	0	5	0	1		
	8	0	87	2	119	1	36	1·371	0·17038
	9	0	11	0	19	0	2		
	10	2	213	0	322	0	61	−1·672	0·09452
Standardised risk ratio for all groups		1·000		1·435		1·846		2·942	0·00326

*Occupation: 1—Professional and technical workers; 2—managers and officials; 3—clerical and related workers; 4—sales workers; 5—farmers, lumbermen, and fishermen; 6—workers in mining and quarrying occupations; 7—workers in transport and communicating occupations; 8—craftsmen, production process workers, and labourers; 9—service workers; 10—not classifiable and not reported.

TABLE II—*Observed and expected deaths from lung cancer in non-smoking women with smoking husbands*

	Observed	Expected	Difference	Ratio	χ^2	
Japan (Hirayama)	142	85·8	+56·2	+65·5%	36·81	Significant
USA (Garfinkel[1])	88	75·3	+12·7	+16·9%	2·14	Not significant
Greece (Trichopoulos *et al*[2])	29	12·1	+16·9	+139·7%	23·60	Significant
Total	259	173·2	+85·8	+49·5%	42·50	Significant

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clearly inadequate for the purposes at hand. Rather fine categorisation is used for husband's occupation, but analysis of the data does not indicate that this is a significant predictor. The stratification for age, on the other hand, is far too coarse. Variations of cancer incidence within 10-year age ranges are large compared with the variations attributed to the husband's smoking. Even relatively small differences in the age distribution of the three populations could thus produce the reported apparent effect. The use of husbands' rather than wives' ages for stratification compounds the problem.

The measure of risk is also inappropriate for a study of such extended duration. The number of person years at risk rather than the number of subjects should be used as the exposure variable, since many subjects would have died of other causes during the study. The appropriate procedure for analysing data of this type is given in Mantel's original paper.[1]

Finally, it is clear from the original paper that Dr Hirayama analysed several causes of death, but reported statistics only for lung cancer. The procedure of reporting only the most significant result from a choice of several possible dependent measures a posteriori is a common error which naturally leads to inflated estimates of significance. Only an appropriate multivariate test can properly estimate statistical significance in this situation.

The analysis reported must thus be regarded as inconclusive unless more refined analyses are able to confirm the results. We endorse the author's suggestion that further study based on larger samples is needed, but we emphasise that such studies can be useful only if the relevant biomedical data are recorded and analysed in sufficient detail to isolate the hypothesised effect from confounding factors.

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[1] Mantel N, Halperin M. *Journal of the American Statistical Association* 1963;58:611-27.

SIR,—Most of the questions raised in my letter (3 October, p 917) were not addressed in the response of Dr Hirayama that followed. The first readings of his original paper troubled me in view of his recognised work, so that before I commented I reviewed every Hirayama paper in the literature on this study population to see if the collective information might answer the questions. A map of Japan was constructed by prefectures and minor population subdivisions and the areas of the study were marked as nearly as they could be ascertained. Review of the reports on the epidemiology and clinical aspects of lung cancer of other Japanese scientists and finally a serious study of Japanese demography, industry, disease trends, and all pertinent data were made; so the questions asked were serious and responsible.

Dr Hirayama did not answer the question about how or why the specific health stations surveyed were selected, or how the few prefectures of the total in Japan from which the health stations were chosen were selected. He admitted that the selection was not random and states, "The satisfactory representativeness of the sample was confirmed after the survey." He does not say by what criteria this was confirmed.

Mapping of the areas selected for study and of the industrial concentrations shows them to be related in nearly every instance. Dr Hirayama states, "Asbestos exposure is quite unlikely to have influenced our result since the proportion of industrial areas are surely not in excess in our sample." Asbestos and other industrial exposures would have to be considered according to the locations of the study areas and of the industrial complexes as revealed on the map of Japan. The areas were nearly all in the areas with high standardised mortality ratios in the excellent and fully documented countrywide epidemiological lung cancer mortality study of Minowa *et al*.[1] The tabulation on the basis of the husbands' ages is not explained. According to the median age at time of marriage in Japan, there is a difference between husbands' and wives' ages, the wives being generally younger. Dr Hirayama states, "We have tables by wives' ages separately." They were not found in the literature search on these data.

No response at all was made to the following questions: (1) Were the families whose medical care was covered by industry omitted from the study? (2) To what population is Hirayama referring? (3) Why were 31% of the women surveyed (and 40% of the women smokers) listed as unknown or not specified as to occupation? For a person to person survey, this suggests methodological problems. (4) Why were references to current Japanese studies by reputable men, Minowa *et al*[1] and Aoki,[2] whose findings did "not seem to explain the prefectural differences of lung cancer mortality" not mentioned? (5) The report by Ishikawa[3] on the preponderance of adenocarcinoma in Japan, in a footnote of which he acknowledges the assistance of Dr Hirayama, his colleague as a reviewer, is not referred to in the answer, although this is very important to this discussion.

Two new issues were introduced by Dr Hirayama in his response, one on the quantity of sidestream smoke inhaled by the wives, without any discussion of the quantity smoked in houses or in the presence of the wives. All the sidestream smoke of husbands' cigarettes would not be inhaled. A remarkably careful study on this subject was reported in 1978 by a French group that helps to explain the differences reported by different techniques of measurement. They improved and explained each innovation they used to overcome logistical problems noted in previous studies. They concluded, with valid proof, that on the strictly toxicological level there is no hazard for non-smokers. The report does not neglect to remark on the problems that are presented to a very important fraction of the population, however. The second issue introduced in the reply was that inhalation through the nose is different from the smoker's direct inhalation. This did not consider the superb filtering system, which would conceivably reduce the amount of ambient smoke inhaled by the wives.[4]

Finally, the far-reaching implications of this unproved passive smoking effect are already in evidence in the literature.

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[1] Minowa M, Shizematsu I, Nagai M, Fukutomi K. *Soc Sci Med* 1981;15D(1):225-31.
[2] Aoki K, Ohno Y. *Nippon Rinsho* 1980;38:2541-50.
[3] Ishikawa S. *Jpn J Clin Oncol* 1973;3:19-30.
[4] Badre R, Guillerm R, Abran N, Bourdin M, Dumas C. *Annales Pharmaceutiques Françaises* 1978;36:443-52.

SIR,—Dr T Hirayama (17 January, p 183) reports a greater risk of lung cancer in non-smoking women when their husbands smoke than when they do not. Assessing the statistical significance of this association by a χ^2 trend statistic on one degree of freedom, Dr N Mantel (3 October, p 914) showed that a non-significant value of 3·31 is obtained if age and occupation are ignored. However, if these factors are taken into account, on the basis of data given in table I of Dr Hirayama's recent letter (3 October, p 916), a higher χ^2 value of 8·70 is obtained, which is statistically significant ($p<0·01$), and similar to, though not identical with, to the value of 10·88 given in his original paper. While this slight discrepancy might have been due, perhaps, to the use of narrower age bands in Dr Hirayama's original calculations, it is clear that the much more significant differences claimed in tables II and III of his letter are due to a statistical error.

Table II, which gives a very much higher χ^2 value of 36·81 for a similar comparison, is based on the false assumption that the lung cancer rate of non-smoking women with husbands who did not smoke is known precisely. The correct calculation, given in my table, gives a much lower level of significance for the Japanese data, and his calculations for the American[1] and Greek[2] data are similarly in error. Consideration only of women with smoking husbands has also led Dr Hirayama to conclude incorrectly that the American study was materially less powerful than the Japanese study because of sample size. In fact, the studies were of very similar power, a slightly smaller total number of deaths in the American study (153 compared with 174) being balanced by the greater stability of the denominator in the relative risk calculations, due to the greater number of deaths in women whose husbands did not smoke (65 compared with 32).

The source of the error in his table III is not clear, but the remarkably narrow 95% confidence bands for relative risk given in the table below the figure cannot be even approximately correct. How, for example, can the ratio of 2·94 given for the comparison of lung cancer rates between non-smoking men whose wives smoke (seven deaths out of 1010) and non-smoking men whose wives do not smoke (50 deaths out of 19 279) possibly have 95% limits as close together as 2·65 and 3·26—that is, ±10%—when the 95% limits for the seven observed deaths are approximately 2 and 12—that is, ±70%—and the variability of the relative risk must be greater than this?

Hugod, *et al*[3] have shown that under quite extreme passive smoke conditions, sufficient to produce a carbon monoxide air concentration of 20 parts per million, a non-smoker would take 11

Observed and expected deaths from lung cancer in non-smoking women in the Japanese study according to the smoking habit of their husbands

	Husbands do not smoke		Husbands smoke			
	Observed	Expected	Observed	Expected	χ^2	p
As given by Hirayama	32	(32·0)	142	85·8	36·81	<0·00001
Correct calculation	32	45·8*	142	128·2*	5·78	<0·05

* Standardised for age and occupation on the basis of data in table I of Dr Hirayama's letter (3 October, p 916).

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PASSIVE SMOKING

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Summary—Before 1980 the argument that passive smoking was a serious health hazard was rather tenuous. It was claimed that it produced allergic reactions, impaired driving ability, reduced exercise tolerance in patients with cardiorespiratory disease and increased the risk of bronchitis and pneumonia in first-year children. However, none of these claims provided convincing evidence relevant to the normal healthy adult nonsmoker. Many studies indicate that nonsmokers are unlikely to inhale more than a very small amount of those components of tobacco smoke traditionally considered harmful. It was surprising, therefore, when a study carried out in the USA showed reduced airways function and studies from Japan and Greece showed an increased lung cancer incidence, in nonsmokers passively exposed to tobacco smoke in comparison with nonsmokers not so exposed. A review of the detail of these studies suggests that none provides conclusive evidence that passive smoking is seriously harmful, a view supported by a recent large study that was carried out in the USA and in which no significant relationship was found between passive smoking and lung cancer. More research is urgently needed, particularly to explore the influence of potentially confounding factors.

Introduction

Passive smoking is the inhalation of tobacco smoke other than by puffing on a cigarette, cigar or pipe. Study of it is relatively new, with few literature references before 1970. In this review a number of types of accusations that had been levelled against passive smoking up until 1979 are considered first. There follows a section summarizing the dosimetric aspects, understanding of which is fundamental to sensible evaluation of the epidemiological evidence, and then recent suggestions that passive smoking might be a more serious health hazard than hitherto considered likely are examined critically.

Early claims

Annoyance and irritation

That passive smoke exposure, especially under conditions of poor ventilation, can be annoying and irritating is a matter of common experience. By interviewing 250 nonallergic patients about their reaction to cigarette smoke, Speer (1968) found that 69% reported eye irritation, 32% headache, 29% nasal symptoms and 25% cough. Weber, Jermini & Grandjean (1976) found that the frequency of reported eye, nose and throat irritation increased with increasing concentrations of smoke in a sealed chamber and suggested that acrolein was the major offending substance. Subsequently, however, Hugod, Hawkins & Astrup (1978) showed that, although a gas-phase polluted atmosphere was as annoying as one polluted with whole sidestream smoke, air pollution with acrolein at three times the concentration present in sidestream smoke caused considerably less discomfort.

Allergy

The 1979 US Surgeon-General's Report (US Public Health Service, 1979) devoted a chapter to the subject of allergy and tobacco smoke. It concluded that the existence of such an allergy was not clearly established but that those with a history of allergies to other substances, especially those with rhinitis or asthma, were more likely to report the irritating effects of tobacco smoke. Whether this was a psychological, rather than a physiological, response is open to question.

Bronchitis and pneumonia in children

Colley (1974), who has been studying respiratory symptoms in children and young adults for many years, first reported evidence of a possible effect of parental smoking in 1974. In this study a slightly increased prevalence of cough in children aged 6–14 years whose parents smoked lost its significance when parental respiratory disease was taken into account. The author noted that "there was no suggestion that exposure to the cigarette smoke generated when parents smoked had any more than a small effect upon the child's respiratory symptoms".

Later in that year Colley, Holland & Corkhill (1974) published a follow-up paper showing that in children in the first year of life, but not in the second to fifth year, prevalence of cough was significantly higher in children of parents who smoked. This excess was still significant if the analysis was restricted to those parents who did not have phlegm. Despite noting that "the association could be a result of shared genetic susceptibility to respiratory disease between parents and children, to living in the same home environment, and to cross-infection within the family"

Abbreviations: CET = Cigarette equivalent time; COHb = Carboxyhaemoglobin; FEF (25–75%) = forced mid-expiratory flow; FEF (75–85%) = forced end-expiratory flow; FEV = forced expiratory volume in 1 second; FVC = forced vital capacity; NDMA = *N*-nitrosodimethylamine; PM = particulate matter.

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they concluded that "a picture has thus emerged of a serious risk to infants in the first year of life from exposure to their parents' cigarette smoke".

A further study by Leeder, Corkhill, Irving *et al.* (1976) sustained these findings, demonstrating an increased prevalence of bronchitis, pneumonia and wheeze (but not asthma) in the first year of life in children whose parents smoked. More possible explanatory factors were studied than in 1974, including whether or not a sibling had symptoms, but standardizing for these did not affect the conclusions.

Whether passive smoke in the atmosphere of the home is the cause of these infections remains open to question. The 1979 US Surgeon-General's Report (US Public Health Service, 1979) suggested that parental neglect may play a role. Also the fact that smokers are more sociable (Eysenck, 1965) could present more opportunity for the children to come into contact with infection.

Psychomotor effects

There has been some concern that relatively low levels of carbon monoxide may have an effect on psychomotor functions, especially in relation to driving a car. The literature reports a great discrepancy in the level at which blood carboxyhaemoglobin (COHb) may affect vigilance. Summarizing the literature, the 1979 US Surgeon-General's Report (US Public Health Service, 1979) concluded that effects seen at levels of COHb found in passive smoking conditions are measurable only at the threshold of stimuli perception and that effects of CO on driving performance and interactive effects of CO and alcohol are only found at higher COHb levels. A recent study by Guillerm, Radziszewski & Caille (1978), in which subjects drove a specially equipped car for 5 hours during the night, exposed either to air or CO sufficient to produce blood levels of 7 or 11% COHb, found no effect of even 11% COHb on driving precision or visual reaction time. This COHb level exceeds that achieved by all passive and indeed most active smokers.

Exercise tolerance

Aronow (1978) examined the effect of passive smoke exposure on 10 patients (two smokers, eight nonsmokers) with angina pectoris. Mean time of exercise until onset of angina in control conditions (COHb level 1·3%) was reduced by 22% after exposure to passive smoke in a ventilated room (COHb level 1·8%) and by 38% after exposure in an unventilated room (COHb level 2·3%). He also noted that the passively exposed patients had a raised heart rate and blood pressure. He attributed this to the possible absorption of nicotine, though he did not measure blood levels. The 1979 US Surgeon-General's Report (US Public Health Service, 1979) considered it unlikely that the very low levels of nicotine absorption could be responsible for these physiological changes and suggested that the response could be due to stress following anxiety or aggravation induced by the smoke-filled room.

Summary of evidence available in 1979

Taking all this evidence together, it seemed clear that, while smoking was a source of annoyance to some, although not perhaps very annoying for many, the grounds for believing it to be a health hazard were rather thin. Where adverse effects were claimed they did not apply to the normal healthy adult nonsmoker and/or were not backed by particularly solid evidence. A statement made in a leading article in the *British Medical Journal* (1978) typified the generally accepted view at the time: "For the moment most—but not *all*—of the pressure for people (including many smokers) to have the right to breathe smoke-free air must be based on aesthetic considerations rather than on known serious risks to health".

Dosimetry

General

A number of totally misleading statements have been made about the dose received by a passive smoker. One example is that by Repace & Lowrey (1980) who, using a theoretical model combined with measurements of cigarette smoke particulate matter (PM) in various different environments, estimated that a nonsmoking office worker exposed to moderate passive smoke inhales the equivalent, in PM terms, of five cigarettes a day while a very heavily exposed nonsmoking musician working in a night club with a chain smoker for a room-mate inhales the equivalent of 27 cigarettes a day. Study of the detail of this paper revealed that the authors had used an extremely low yielding cigarette with a PM yield of only 0·55 mg/cigarette as a basis for calculating cigarettes per day. If, more realistically, a sales weighted average cigarette with a PM yield of 17·6 mg/cigarette had been used, the appropriate exposures would have become one-sixth of a cigarette per day for the office worker and five-sixths of a cigarette per day for the musician. Even more outlandish was the recently reported claim of Lane quoted in the national press in the UK (*Daily Mail* and *Daily Telegraph* both of 2 June 1981) that "there is now medical evidence to show that the smoke breathed in by non-smokers is 18 times higher in tar and 12 times higher in nicotine than the smoke breathed by smokers...". The source of this claim undoubtedly comes from a table published by the Laboratory of the Government Chemist (1980), which showed that the ratio of sidestream to mainstream yields was 18 for tar and 12 for nicotine when a very low tar cigarette was smoked under machine conditions. Not only had the cigarette used as a basis for comparison a tar level some 10 to 15 times less than that normally smoked, but the fundamental error of confusing sidestream yields and ambient concentrations had also been made. The concentration of sidestream smoke is measured as it leaves the burning cone of tobacco between puffs, whereas what is relevant to the passive smoker is the concentration of smoke as it reaches him after dilution by room air. Ambient concentrations vary drastically depending on the degree of room ventilation but even under conditions of poor ventilation will be very considerably less than sidestream concentrations, which a nonsmoker would only receive if he were to keep his nose right on top of the cigarette.

A number of workers have measured the concentration of smoke constituents in ambient air and in body fluids. An important study by Hugod *et al.* (1978) measured air concentrations of a number of

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Table 1. *Comparison of uptake of smoke constituents in smokers and passive smokers**

Smoke constituent	Mainstream yield inhaled by smoker (mg/cigarette)	Inhaled amount in passive smoking conditions (mg/hr)†	Cigarette equivalents/hr	Cigarette equivalent time (hr)
NO	0·30	0·182	0·61	1·6
CO	18·40	9·160	0·50	2·0
Aldehyde	0·81	0·214	0·26	3·8
Acrolein	0·09	0·013	0·14	7·1
TPM	25·30	2·300	0·09	11·1
Nicotine	2·10	0·041	0·02	50·0
Cyanide	0·25	0·005	0·02	50·0

TPM = Total particulate matter

*Data from Hugod, Hawkins & Astrup (1978).

†Volunteers were exposed in a closed, unventilated room to quite severe passive smoke conditions in which the air CO concentration was kept at 20 ppm over a 3-hr period.

constituents in a closed, unventilated room in which ten volunteers were exposed to quite severe passive smoke exposure conditions in which the air CO concentration was kept at 20 ppm. Comparing the estimated inhaled amounts of each constituent with those inhaled by a smoker they calculated cigarette equivalent times (CET) in hours for seven different constituents (Table 1). It can be seen that these estimates of the time taken to inhale the equivalent of one cigarette vary widely according to the particular constituent.

Nicotine

For nicotine, Hugod *et al.* (1978) estimated it would take a passive smoker 50 hr to take in as much as would a smoker smoking one cigarette, an amount they regarded as negligible. Their results are broadly consistent with those of Hinds & First (1975) who estimated that nicotine concentrations in various public places in the USA ranged from the equivalent of one-thousandth of a filter cigarette per hour in a "bus station waiting room up to almost one-hundredth in a cocktail lounge. Similarly Russell & Feyerabend (1975) found that nonsmokers exposed experimentally in an almost intolerably smoky room, whilst having average urinary nicotine levels almost ten times higher than nonsmokers not deliberately exposed to smoke, had urinary nicotine levels 15 times lower than average smokers.

Total particulate matter

For total particulate matter, the constituent usually considered to be related to the excess of lung cancer risk in smokers, Hugod *et al.* (1978) concluded that the CET value is "so high that the passive smoker will never inhale more than what equals ½–1 cigarette per day"—a finding consistent with the conclusions of Repace & Lowrey (1980) if adjusted so that a sensible baseline cigarette is used for comparison.

Carbon monoxide

For CO, the conclusions of Hugod *et al.* (1978) are similar to those of Russell, Cole & Brown (1973) who, working with even more extreme conditions involving twice the exposure level for CO than that used by Hugod *et al.*, found half the CET value (i.e. 1 hour). Even despite this relatively low CET value, it is most unlikely that passive smokers will achieve blood COHb levels as high as 3% which has been claimed to decrease the threshold for intermittent claudication and angina pectoris in patients with obliterating arterial disease (Anderson, Andelman, Strauch *et al.* 1973; Aronow, Stemmer & Isbell, 1974).

N-Nitrosodimethylamine

N-Nitrosodimethylamine (NDMA) merits mention in the context of passive smoking because of its unusually high ratio of sidestream to mainstream smoke deliveries (Brunnemann, Fink & Moser, 1980) and of its known biological activity.

Brunnemann, Adams, Ho & Hoffmann (1978) measured the levels of NDMA in the atmosphere for several indoor locations in the USA. The highest concentration found (0·24 ng/litre) was in a bar, and the authors calculated that a nonsmoker in this situation would inhale, in 1 hour, an amount of NDMA equivalent to that inhaled by a person actively smoking 17–35 filter cigarettes. Not only was this an extremely smoky atmosphere (their equivalent figure in a bank, where smoking was permitted, being one to two filter cigarettes), but the concentration considerably exceeded that (0·07 ng/litre) found by H. Altmann (personal communication, 1981) in a small (46 m^3) unventilated conference room in which 11 people smoked 64 cigarettes in 2 hours—conditions sufficient to produce nausea in the majority of those present. The significance of these low levels of NDMA is not clear. The 1979 US Surgeon-General's Report (US Public Health Service, 1979) points out that the absorption of nitrosamine from environmental conditions is not necessarily equivalent to the absorption by smoking, while Brunnemann *et al.* (1980) have emphasized that "no epidemiological data exist linking human respiratory cancers to volatile nitrosamines".

Dosimetry—a conclusion

Hugod *et al.* (1978) concluded that "in spite of an often considerable subjective discomfort, exposing non-smokers to tobacco smoke under realistic conditions will not cause inhalation of such amounts of the components of tobacco smoke traditionally considered harmful, that a lasting, adverse health effect in otherwise healthy, grown-up individuals seems probable".

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Table 2. *Vital capacities and expiratory flow rates in smokers and nonsmokers**

Sex	Group number	Smoking habits†	Percentage of predicted			
			FVC	FEV_1	FEF 25–75%	FEF 75–85%
Male	1	Nonsmokers, no smoky environment	102	103	104	120
	2	Nonsmokers, smoky environment	99	98	91	95
	3	Smokers not inhaling	96	99	92	87
	4	Smokers: 1–10 cigarettes/day	95	97	89	77
	5	Smokers: 11–39 cigarettes/day	84	86	76	68
	6	Smokers: >40 cigarettes/day	82	77	72	60
Female	1	Nonsmokers, no smoky environment	102	104	108	112
	2	Nonsmokers, smoky environment	98	99	93	85
	3	Smokers not inhaling	97	99	92	85
	4	Smokers: 1–10 cigarettes/day	96	98	89	83
	5	Smokers: 11–39 cigarettes/day	85	85	78	69
	6	Smokers: >40 cigarettes/day	78	80	72	62

*Data from White & Froeb (1980).

†Exposure to a smoky environment or consumption of cigarettes was for more than 20 yr. Group 3 includes pipe, cigar or cigarette smokers who did not inhale. Groups 4, 5 and 6 were all inhaling cigarette smokers.

Newer evidence

Effects on the small airways

In the last 2 years, some new evidence has caused a considerable amount of rethought on the passive-smoking issue. The first such evidence, published in the *New England Journal of Medicine* in March 1980, came from a study by White & Froeb (1980) of the relationship between various pulmonary function indices and passive smoking. A group of 3002 men and women who had been physiologically evaluated during a "physical fitness profile" course, and who were without a history of relevant cardiorespiratory disease, occupational exposure to dust or fumes or severe exposure to pollution at home or at work were divided into six groups according to their exposure to tobacco smoke. No significant difference was found between nonsmokers exposed to a smoky environment for more than 20 years (group 2) and nonsmokers never so exposed (group 1) as regards forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1); but nonsmokers exposed to passive smoke had statistically significant reductions in forced mid-expiratory flow (FEF 25 to 75%) and in forced end-expiratory flow (FEF 75 to 85%; Table 2).

The most surprising thing about the results of White & Froeb (1980) was that the reductions in FEF seen in group 2 were generally very similar to those seen in group 4, smokers of one to ten cigarettes per day for more than 20 years. Why should a relatively large difference (group 2 *v.* group 1) in airways dysfunction be seen as a result of an apparently relative small difference in exposure to smoke constituents when only a relatively small difference (group 4 *v.* group 2) is seen in response to what was in all probability a much larger difference in exposure?

In view of this implausible result considerable attention had to be given to the details of the study and a number of criticisms were voiced in the *New England Journal of Medicine* (Adlkofer, Scherer & Weimann, 1980; Aviado, 1980; Huber, 1980). One of the oddest things about the study was the procedure by which the sample was selected. It was stated that each candidate was classified into one of the six defined groups. Yet it is clear from Table 2 that anyone who changed smoking habits in the last 20 years does not fit into any group. Furthermore, as the authors define both groups 1 and 2 as living in a house where tobacco smoking was not permitted, what has happened to those nonsmokers, presumably in the great majority, who lived in a house where it was permitted? There are other less important omissions too (inhaling pipe and cigar smokers or cigarette smokers not allowed to smoke at work) and one might even consider it harder to find people who do fit into the groups of White & Froeb (1980) than to find ones who do not. Without an adequate explanation of this anomaly, it is difficult to have much confidence in these findings.

Lung cancer

Whilst the findings of White & Froeb (1980) relate to an index which is contentious and certainly not an accepted reliable indicator of an increased health risk, two more studies published in January 1981, by Hirayama (1981a) and by Trichopoulos, Kalandidi, Sparros & McMahon (1981), caused more attention, as both claimed that nonsmoking wives of smokers had a significantly greater risk of lung cancer than nonsmoking wives of nonsmokers.

Japanese study. Of the two studies, that by Hirayama (1981a), who followed up 91,540 Japanese nonsmoking married women aged 40 years or over in 1965 for 14 years, is the more substantial. He classified women into three groups according to the smoking habits of the husband. The results showed a highly significant trend in the risk of lung cancer with increasing smoking by the husband, with wives of heavy smokers having double the risk of wives of nonsmokers (Table 3). In contrast the wives of smokers had no significant increase in risk for emphysema, asthma, ischaemic heart disease, or cancer of the cervix or stomach.

Following critical comments by Grundmann, Müller & Winter (1981), Kornegay & Kastenbaum (1981), Macdonald (1981), Rutsch (1981) and Sterling (1981), further information on the detail of his study has been given by Hirayama (1981b, 1981c). It is useful to summarize briefly the main points raised and to consider their implications.

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Table 3. *Age-occupation standardized lung cancer risk in Japanese women nonsmokers**

Smoking habit of husband	Sample size	Number of lung cancer deaths	Annual lung cancer mortality rate per 100,000	Standardized lung cancer risk ratio	Significance of trend
Nonsmokers or occasional smokers	21,895	32	8·7	1·00	-
Ex-smokers or smokers of 1–19 cigarettes/day	44,184	96	14·0	1·61	χ^2 = 10·88†
Smokers of ⩾ 20 cigarettes/day	25,461	56	18·1	2·08	P = 0·001

*Data from Hirayama (1981a).
†One degree of freedom test statistic scoring 0, 1 and 2 for the three smoking categories.

(1) It was suggested that the statistically significant χ^2 value of 10·88 shown in Table 3 might be the result of an arithmetical error as calculations by Mantel (1981), based on the unstandardized data given in the original paper, gave a χ^2 value of only 3·31 which was not significant. In fact the confusion appears to have arisen because Hirayama (1981a) had standardized for age and occupation but had not stated this clearly. This was important as the husbands who smoked were younger than those who did not. In a subsequent letter Hirayama (1981c) presented data by age and occupation which allowed one to calculate a χ^2 value of 8·70 which, while not the same as that originally quoted, was similar and significant. Surprisingly, in the same letter, Hirayama (1981c) quoted a much higher χ^2 value of 36·81 for a similar comparison (difference between nonsmoking women whose husbands have never smoked and those whose husbands have ever smoked) but this was based on a statistical error (Lee, 1981). Despite this error, it seems probable that the association found really was a significant one, though of course a significant association need not imply a significant causal effect of passive smoke exposure.

(2) For a reason that was not apparent, Hirayama (1981a) standardized for age of the husband and not for the age of the wife. However it seems unlikely this would have materially affected the findings, as, if it did cause bias, it would be expected to affect all the causes of death and not just lung cancer.

(3) Smoking habits were determined only at the beginning of the period and may have changed. Again, however, it seems unlikely that enough of these women would have taken up smoking to cause marked bias.

(4) The great majority of the lung cancers seen, 17 out of 23 in a sample, were adenocarcinomas, a type of lung cancer generally believed to be much more weakly related to smoking than squamous cell carcinoma.

(5) Evidence of trends in lung cancer rates in Japan suggest that there may be some other important cause of lung cancer which was not studied. Between 1947 and 1978, female lung cancer rates rose nine-fold and yet Hirayama's (1981a) own results show only a four-fold risk in active cigarette smokers compared with non-passively exposed nonsmokers—and relatively few women in Japan (about 15%) smoke anyway.

(6) The index of "passive" exposure used is not likely to be very accurate. Not only does the husband smoke a varying proportion of his cigarettes at home, but the wife will also be exposed to other sources of exposure besides the husband. In principle, though, this is likely to underestimate rather than overestimate any relative risk associated with passive smoking.

(7) What is most surprising, however, is the sheer magnitude of the association. The two-fold increased risk in wives of heavier smokers is similar, in Hirayama's (1981a) study, to that of women actively smoking about five cigarettes a day, whilst it was stated that the heavy smokers smoked on average only 8·4 cigarettes a day at home and these presumably not all in the direct presence of the wife. If this is so, the study seems to be suggesting that one actively smoked cigarette is not so very different from one passively smoked one, which seems completely inconsistent with the dosimetry, especially when one realises that an active smoker probably has greater passive smoke exposure than a passively exposed nonsmoker.

Greek study. In contrast to the Japanese study, the small Greek case-control study of Trichopoulos *et al.* (1981) is relatively lightweight, being based on only 40 lung cancer cases seen in nonsmoking women. However, their results (Table 4), though having quite wide confidence limits, agree well with those of Hirayama (1981a). Taking into account a number of possible confounding factors (age, duration of marriage, occupation, schooling, residence) did not affect the general picture.

Although the trend is statistically significant, the limitations pointed out by the authors—the small number of cases, 35% of which were not cytologically confirmed, and the cases and controls being taken from different hospitals—would have meant that no great weight would have been attached to the results had they not come out at the same time as, and being supported by, those of Hirayama (1981a). It is interesting, in comparison with the Japanese study, that Trichopoulos *et al.* (1981) specifically excluded adenocarcinomas from their cases, since it was presumably implicitly assumed that this type of lung cancer was not smoking-associated.

American study. Even taken together, the Japanese and Greek studies are by no means totally convincing. Doubts as to whether such a large effect on lung cancer incidence could possibly be due to such an apparently small dose of tobacco smoke have very recently been supported by Garfinkel (1981) based on

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Table 4. *Smoking habits of husbands of Greek nonsmoking women with lung cancer and of nonsmoking control women**

Smoking habit of husband		Lung cancer cases	Controls	Relative risk	Significance of trend
Nonsmokers		11	71	1·0	
Ex-smokers		6	22	1·8	
Smokers (cigarettes/day):	1–10	2	9	2·4	$\chi^2 = 6{\cdot}45$
	11–20	13	32		
	21–30	4	6	3·4	$P < 0{\cdot}02$
	>30	4	9		
	Total...	40	149		

*Data from Trichopoulous, Kalandidi, Sparros & MacMahon (1981).

results from the American Cancer Society's million person prospective study and the US Veterans Study. Two analyses were carried out. The first, similar to that used in the Japanese and Greek studies, showed no significant relationship between lung cancer risk and the smoking habit of the husband (Table 5). Indeed, after matching for age, occupation, education, race, urban/rural residence and absence of serious disease at the start of the study, nonsmoking women married to smokers of 20 or more cigarettes a day had an estimated risk of lung cancer virtually identical to that of non-smoking women married to non-smokers.

The second analysis found no evidence of any trend in lung cancer rates in nonsmokers over the period of either study. As death rates of smokers had increased substantially over the period, presumably mainly because of the duration of smoking effect (older smokers at the end of the period would on average have smoked for longer than similar aged smokers at the beginning of the period), one might have expected a similar rise to be seen in non-smokers, had passive smoking been a material cause of lung cancer risk in non-smokers.

Although one might argue that passive-smoking effects would be more difficult to pick up in the USA where women spend more time out of the home and marry more often [Garfinkel (1981) had no data on smoking habits of ex-husbands] than is the case in Greece or Japan, it is clear that the Garfinkel (1981) study has underlined the view that further studies are needed to explore the relationship between passive smoking and lung cancer.

Both Garfinkel (1981), and also Hammond & Seli-koff (1981) in a paper reviewing findings from the Japanese and Greek studies, pointed out that it is extremely difficult to reconcile findings indicating a higher risk of lung cancer in passive smoking with results from the study by Auerbach, Garfinkel & Hammond (1979) of histological changes in bronchial epithelium taken from autopsy material. Lesions frequently seen in cigarette smokers (such as atypical nuclei and lesions similar to carcinoma *in situ*) have very rarely been found in people who have never smoked. This finding, and also the reported small doses of smoke received by nonsmokers, both suggest that passive smoking cannot play more than a very small role in the development of lung cancer, a view also reached by Lehnert (1981) who considered evidence from the USA and Japanese studies in detail. If passive smoking is not causally implicated it is of fundamental importance to try to identify the confounding or biassing factors that resulted in the higher risk of lung cancer seen in wives of smokers in the Japanese and Greek studies, but not in the American study.

Conclusion

While more research is certainly needed, there seems at present to be no convincing evidence that passive smoking results in any material risk of serious disease for the healthy nonsmoker.

REFERENCES

Adlkofer, F., Scherer, G. & Weimann, H. (1980) Small-airways dysfunction in passive smokers (Letter). *New Engl. J. Med.* 303, 392.

Anderson, E. W., Andelman, R. J., Strauch, J. M., Fortuin, N. J. & Knelson, J. H. (1973) Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris. A study of ten patients with ischemic heart disease. *Ann. intern. Med.* 79, 46.

Aronow, W. S. (1978) Effect of passive smoking on angina pectoris. *New Engl. J. Med.* 299, 21.

Aronow, W. S., Stemmer, E. A. & Isbell, M. W. (1974)

Table 5. *Lung cancer deaths amongst nonsmoking women in the USA**

Smoking habit of husband	Number of lung cancer deaths	Age standardized analysis mortality ratio	Matched group analysis mortality ratio
Nonsmoker	65	1·00	1·00
Smoker: <20 cigarettes/day	39	1·27	1·37
Smoker: ⩾20 cigarettes/day	49	1·10	1·04

*Data from Garfinkel (1981).

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Effect of carbon monoxide exposure on intermittent claudication. *Circulation* 49, 415.
Auerbach, O., Garfinkel, L. & Hammond, E. C. (1979). Change in bronchial epithelium in relation to cigarette smoking 1955–1960 vs 1970–1977. *New Engl. J. Med.* 300, 381.
Aviado, D. M. (1980). Small-airways dysfunction in passive smokers (Letter). *New Engl. J. Med* 303, 393.
British Medical Journal (1978). Breathing other people's smoke. *Br. med. J.* 2, 453.
Brunnemann, K. D., Adams, J. D., Ho, D. P. S. & Hoffmann, D. (1978) The influence of tobacco smoke on indoor atmospheres. II. Volatile and tobacco specific nitrosamines in main and sidestream smoke and their contribution to indoor pollution. *Proceedings, 4th Joint Conference of Sensing of Environmental Pollutants, New Orleans, Louisiana, 1977*, p. 876. American Chemical Society.
Brunnemann, K. D., Fink, W. & Moser, F. (1980). Analysis of volatile N-nitrosamines in mainstream and sidestream smoke from cigarettes by GLC-TEA. *Oncology* 37, 217.
Colley, J. R. T. (1974). Respiratory symptoms in children and parental smoking and phlegm production. *Br. med. J.* 2, 201.
Colley, J. R. T., Holland, W. W. & Corkhill, R. T. (1974). Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. *Lancet* II, 1031.
Eysenck, H. J. (1965). *Smoking, Health and Personality*. Weidenfeld and Nicholson, London.
Garfinkel, L. (1981). Time trends in lung cancer mortality among non-smokers and a note on passive smoking. *J. natn. Cancer Inst.* 66, 1061.
Grundmann, E., Müller, K.-M. & Winter, K. D. (1981). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 282, 1156.
Guillerm, R., Radziszewski, E. & Caille, J. E. (1978). Effects of carbon monoxide on performance in a vigilance task (automobile driving). In *Smoking Behaviour: Physiological and Psychological Influences*. Edited by R. E. Thornton p. 148. Churchill Livingstone, Edinburgh.
Hammond, E. C. & Selikoff, I. J. (1981). Passive smoking and lung cancer with comments on two new papers. *Envir. Res.* 24, 444.
Hinds, W. C. & First, M. W. (1975). Concentrations of nicotine and tobacco smoke in public places. *New Engl. J. Med.* 292, 844.
Hirayama, T. (1981a). Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br. med. J.* 282, 183.
Hirayama, T. (1981b). Passive smoking and lung cancer (Letter). *Br. med. J.* 282, 1393.
Hirayama, T. (1981c). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 283, 916.
Huber, G. L. (1980). Small-airways dysfunction in passive smokers (Letter). *New Engl. J. Med* 303, 392.
Hugod, C., Hawkins, L. H. & Astrup, P. (1978) Exposure of passive smokers to tobacco smoke constituents. *Int. Archs occup. envir. Hlth* 42, 21.
Korndegay, H. R. & Kastenbaum, M. A. (1981). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 283, 914.
Laboratory of the Government Chemist (1980). *Report of the Government Chemist 1979*. Department of Industry. HMSO, London.
Lee, P. N. (1981). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 283, 1465.
Leeder, S. R., Corkhill, R., Irving, L. M., Holland, W. W. & Colley, J. R. T. (1976). Influence of family factors on the incidence of lower respiratory illness during the first year of life. *Br. J. prev. soc. Med.* 30, 203.
Lehnert, G. (1981). Krank durch Passiv-rauchen? *Münch. med. Wschr.* 123, 1485.
Macdonald, E. J. (1981). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 283, 915.
Mantel, T. (1981). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 283, 914.
Repace, J. L. & Lowrey, A. H. (1980). Indoor air pollution, tobacco smoke, and public health. *Science, N.Y.* 208, 464.
Russell, M. A. H., Cole, P. V. & Brown, E. (1973). Absorption by non-smokers of carbon monoxide from room air polluted by tobacco smoke. *Lancet* I, 576.
Russell, M. A. H. & Feyerabend, C. (1975). Blood and urinary nicotine in non-smokers. *Lancet* I, 179.
Rutsch, M. (1981). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 282, 985.
Speer, F. (1968). Tobacco and the nonsmoker. A study of subjective symptoms. *Archs envir. Hlth* 16, 443.
Sterling, T. D. (1981). Non-smoking wives of heavy smokers have a higher risk of lung cancer (Letter). *Br. med. J.* 282, 1156.
Trichopoulos, D., Kalandidi, A., Sparros, L. & MacMahon, B. (1981). Lung cancer and passive smoking. *Int. J. Cancer* 27, 1.
US Public Health Service (1979). *Smoking and Health. A Report of the Surgeon-General*. US Department of Health, Education and Welfare. DHEW Publ. No. (PHS) 79-50066.
Weber, A., Jermini, C. & Grandjean, E. (1976). Irritating effects on man of air pollution due to cigarette smoke. *Am. J. publ. Hlth* 66, 672.
White, J. R. & Froeb, H. F. (1980). Small-airways dysfunction in nonsmokers chronically exposed to tobacco smoke. *New Engl. J. Med.* 302, 720.

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AGE AS A MODIFYING FACTOR IN THE ASSOCIATION BETWEEN LUNG CANCER IN NON-SMOKING WOMEN AND THEIR HUSBANDS SMOKING STATUS

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ABSTRACT:

A previous analysis (1) of (2) is reviewed and extended. Age is shown to be an important modifying factor in the association between lung cancer in nonsmoking women and their husbands' smoking status. Heterogeneity of the cell specific risk ratios is demonstrated using the Mantel-Haenszel extended test for trend, when the data are stratified by the wife's age. The lack of fit of the multiplicative model contra-indicates the use of a Mantel-Haenszel summary statistic. It is likely that age at entry is confounded with calendar period increases in lung cancer mortality in nonsmoking women.

INTRODUCTION

Hirayama reports (2) on a longitudinal record linkage study of married women who, in 1965, were reported to be nonsmokers. Deaths in the period 1966 to 1981 were linked to a questionnaire given in 1965. In this manner, the cause of death in those women who had died by 1981 was linked to the initial interview in 1965 of both husband and wife to produce the results reported (2). His paper presents the mortality experience of nonsmoking wives by selected causes of death cross-classified by husband's smoking status, husband's drinking status, husband's occupation, green and yellow vegetables daily and husband's age. Here, we restrict our attention to Tables 1 & 2 of (2) in order to focus on the effect of standardising by husband's age rather than by the wife's age when studying the association between these women's lung cancer deaths and their husbands' smoking status.

An earlier paper (1), based on a standard Poisson regression and using the conventional 5% level of significance, indicates, on the basis of these published tables, that

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IN: INDOOR AND AMBIENT AIR QUALITY; eds. R. Perry and P. Kirk. Selper Ltd., 1988

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- husband's smoking is marginally associated with wife's lung cancer mortality, the size of the effect being of borderline statistical significance and dependent on the presence or absence of other factors in the model and the classification of the husband's smoking at entry.
- that husband's drinking habit shows no significant association with his wife's lung cancer mortality.
- that daily intake of green/yellow vegetables shows no significant association with lung cancer mortality.

In contrast, it is concluded in (2) that there is 'a significantly increased risk of' lung cancer mortality 'in relation to the extent of the husband's smoking... The association was significant when observed by age of husbands .. and also by age of wives.'

Tables 1 and 2 of (2) give different tabulations of the 16 years lung cancer mortality in these nonsmoking wives. Table 1 gives the lung cancer death rates by five levels of husband's smoking at entry (Non, Ex, 1-14/d, 15-19/d, 20+/d). Table 2 collapses this to Non, Ex. or 1-19/day, 20+/day, here called Non, Light and Heavy ETS exposure. Table 1 further stratifies the wives' lung cancer death rates by the husband's age at entry whereas Table 2 stratifies by the wife's age at entry. (Since it is the usual practice to adjust for the subject's age rather than her husband's, it is remarkable that this is the only occasion in which Dr Hirayama has adjusted wife's mortality by her own age rather than that of her husband's).

Exhibit 1 summarizes a 'power' model analysis of Tables 1 and 2. The power transform finds the best model within a family of loglinear models which include the multiplicative and additive models. Exhibit 1 shows the residual deviance after fitting the factors for age and ETS exposure to Tables 1 and 2 of (2). Table 1 shows little discrimination among models, all giving good fits. Table 2, in contrast, shows that the additive model fits better than the multiplicative model. Indeed, the best fitting power model has a power of $\rho = 1.14$ which is *beyond* the additive for which $\rho = 1.0$. (The multiplicative model in turn corresponds to a $\rho = 0$). However, all models of Table 1 are better fitting than the best fitting model for Table 2, suggesting that further stratification in five year groups may be necessary to adjust for age or that other covariates may be important.

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Exhibit 1

Deviances (df) for additive, multiplicative and best fitting power models

	MODEL		
TABLE	ADDITIVE	POWER	MULTIPLICATIVE
Table 1	3.79 (12)	2.76 (12)	3.24 (12)
Table 2	7.91 (6)	7.85 (6)	10.72 (6)

Model is 1+ Husband's Age(4)+ ETS(5) for Table 1

..... 1+ Wife's Age(4)+ ETS(3) for Table 2

Outcome analyzed is cumulative Lung Cancer Death Rate (1966-1981)

The additive model provided a superior fit when wife's age is used to stratify as in Table 2. This means that risk ratios for ETS exposure change with age at entry. The additive model assumes that a constant excess risk is added to the age dependent death rate from lung cancer. Thus, the substitution of husband's age for wife's age changes the underlying model from the multiplicative to the additive and the appropriate summary statistic from a risk ratio to an excess risk.

The analysis given by (1) of (2) was that recommended by Breslow & Day (3) for cohort studies. Dr Hirayama, however, presents his results in terms of the older and more limited Mantel-Haenszel statistics. Here, we follow (2) in presenting a 'classical' analysis of his results in order to show what Dr Hirayama *might* have reported with the techniques available to him at that time, if the data had been stratified by the subject's age at entry rather than by spousal age.

RESULTS

Hirayama's analysis treats Table 2 as a 2x4x3 contingency table where wives are classified as either having died from lung cancer or not, and are

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then further tabulated in 4 ten year age groups by wife's age in 1965 and by 3 levels of husband's cigarette smoking (as reported in 1965).

He analyzes Table 2 by comparing the base line exposure in each age group, Non with Light and Non with Heavy ETS exposures. In other words, Hirayama treats Table 2 as though it were two 2x2x4 tables.

He then presents point estimates of the summary risk ratio for Table 2, and tests for the significance of the weighted risk ratio but omits tests for the homogeneity of the age-specific risk ratios which form his Mantel-Haenszel estimate. (A significant test of homogeneity indicates that the use of the weighted estimate is contra-indicated in that the age-specific risk ratios differ significantly).

Here, we collapse the five ETS levels in Table 1 to Non, Light and Heavy in order to have a similar configuration to Table 2. Now the only difference between (collapsed) Table 1 and Table 2 is the use of husband's age in Table 1 and the the use of wife's age in Table 2.

Exhibit 2

Table 1 Lung Cancer Risk Ratio (1966–1981)

HUSBAND'S SMOKING

		Non vs Light	Non vs Heavy	Non vs Exposed
	40–49	1.55	2.32	1.87
HUSBAND'S	50–59	1.54	1.90	1.68
AGE AT	60–69	1.53	1.96	1.64
ENTRY	70+79	0.71	0.67	0.70
χ^2_{trend}	df=1	0.34	5.6	0.71
$\chi^2_{common\ \psi}$	df=3	1.39	1.13	2.03
$\chi^2_{\psi_{MH}=1}$	df=1	3.16	8.53	5.70
ψ_{MH}		1.43	1.90	1.57

Using the classical Mantel-Haenszel methodology for stratified data, the results of the power modelling on Table 1 were confirmed. Thus, see Exhibit 2, stratification by husband's age and the three levels of ETS exposure (Non, Ex. or 1-19/day , 20+/day, called Non, Light and Heavy here, yielded risk ratios that were reasonably constant across age strata. Testing the

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homogeneity of the age-specific risk ratios across the four age strata yielded a homogeneity chi-square on 3 degrees of freedom (χ^2_3) that is not significant at either level of the ETS exposure or at both levels combined (Non vs Exposed).

The test of homogeneity in common use is not powerful (4), especially when applied in this manner to cohort data. A more complete treatment of the test for heterogeneity, as applied to cohort studies, is given in (3). Note, however, that we restrict ourselves to the case-control version of the Mantel-Haenszel approach in order to mirror Dr Hirayama's form of analysis.

A test for trend in the risk ratio over age, based on 1 degree of freedom, is provided here for comparability with the analysis which follows. Exhibit 2 shows that the trend test is not significant, with the possible exception of Non vs Heavy (but the value 5.6 is unstable and may be discounted).

Exhibit 3

Table 2 Lung Cancer Risk Ratio (1966–1981)

HUSBAND'S SMOKING

		Non vs Light	Non vs Heavy	Non vs Exposed
	40–49	2.38	3.30	2.76
WIFE'S	50–59	1.60	1.92	1.72
AGE AT	60–69	1.15	1.02	1.12
ENTRY	70–79	0.09	0.48	0.19
χ^2_{trend}	df=1	4.34	5.48	7.64
$\chi^2_{common\ \psi}$	df=3	11.94	5.41	11.24
$\chi^2_{\psi_{MH}=1}$	df=1	2.28	5.15	3.88
ψ_{MH}		1.36	1.66	1.45

In contrast to the above analysis, a strong statistical interaction between age and ETS exposure (Exhibit 3) is evident when the data are stratified by wife's age. The chi square test for homogeneity is statistically significant ($P < .05$) when comparing Non to Exposed across age, as is the comparison between Non and Light ($P < .01$). The comparison between Non and Heavy ETS exposure (20+/day) is not statistically significant. The Mantel-Haenszel extension test to evaluate trends across *age* for each level of the

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husband's smoking status is statistically significant ($P < .05$) at all exposure levels. This indicates a true decrease in the risk ratios with increasing wife's age. Indeed, the statistical significance or P value of the trend over wife's age is of the same order as the trend for a " dose response" relationship between the lung cancer death rate and the husband's smoking status.

These results compare favorably with the results from the more general power analysis. This underscores the need, when doing the classical Mantel-Haenszel analysis, to *first* test the assumption of a common risk ratio before proceeding to use the Mantel-Haenszel summary estimate. If the assumption of a common risk ratio is untenable, it is wrong to proceed to calculate and test the significance of a global estimate. "In this situation, it is more important to try to understand and describe the sources of variation in the relative risk than simply to provide a summary measure" (4, p.138)

Our conclusion, presented at Tokyo, was that the multiplicative model which is implicit in the use of the risk ratio is contra-indicated. The relationship between ETS exposure and lung cancer mortality was demonstrated in these data as best described by the additive model. This leads to 'excess risk' as the appropriate summary statistic.

The lack of fit of the multiplicative model may be seen directly from an examination of the risk ratios by age group. Under the multiplicative model, the risk ratio is assumed to be constant over age, apart from random sampling error. Exhibit 3 shows that the risk ratio falls dramatically with age for Non vs Light, Non vs Heavy and Non vs Exposed. It is unexpected to find such a radical shift in the underlying model, given the stated equivalence in the age structures of husband and wife.

DISCUSSION

The Mantel-Haenszel analysis used in (2) implicitly assumes a multiplicative model. This, in turn, is based on the assumption that the risk ratio for ETS exposure and lung cancer mortality in nonsmoking wives is relatively constant over a 40 year age range in the cohort and over the 16 years of follow-up. This assumption could have been tested in (2) on Table 2 with the techniques available at that time. Here, in our analyses, both the Mantel-Haenszel tests for trend and the commonly used test of homogeneity over strata (4), show a clear indication that the multiplicative model does not hold when the wife's age is used to stratify her cumulative lung cancer mortality covering 16 years.

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Age at entry effects encompass both chronological age and cohort differences. In the light of the current finding that the risk ratio falls with age at entry, it is also likely that risk ratios would be found to fall with calendar time.

If tests for a common risk ratio by wife's age at entry had not been statistically significant, then Dr Hirayama's substitution of husband's age for wife's age would have had few implications. But since this switch has been shown to change the underlying statistical model and summary statistic, it is clear that husband's age cannot be use as a proxy for wife's age. There is indeed no good reason to do so as wife's age was recorded along with husband's age at entry to the study in 1965. Since Table 2 is the only occasion on which the wife's age is given, we cannot investigate possible interactions of wife's age with other covariates used by Dr Hirayama in this study. Other causes of death in women are also stratified by husband's age. Thus, we are unable to verify whether the current anomaly exists for other causes of death. It is therefore unknown whether husband's age is a satisfactory surrogate for wife's age in any of those papers by Hirayama which deal with female mortality.

Lung cancer mortality in these nonsmoking wives has been shown to be low compared with the Japanese population (1). This may be true of all female mortality results from this study.

It has been pointed out (1) that stratification by age into 4 ten year age groups may result in substantial residual confounding. Whether stratification was based on husband's or wife's age is irrelevant, since, when "the stratification is too coarse, ... some confounding may remain" (4, p.99). How much of the interaction identified in Exhibit 3 using wife's age might be attributable to an inadequate control of age is unknown. Further, as a consequence of the poor fit of the multiplicative model in that analysis,age and calendar time interaction cannot be ruled out as contributing to a potentially spurious association between lung cancer mortality and ETS. We affirm Breslow & Day's suggestion (3) that five year age groups be used and, that "for a long study, it is appropriate to partition the time axis into several intervals" (4, p.201). A true cohort study would report the duration of ETS as well as the (presumed) daily exposure and would use each subject's person-years of follow-up as the denominator in rate calculations and risk analysis. From Dr Hirayama's written descriptions of his study, such information is in his files or is available by linking a couple's initial questionnaire and death certificates.

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SUMMARY & CONCLUSIONS

With the exception of Table 2 of (2), husband's age has been used to adjust for wife's mortality in a large and often quoted record linkage study in Japan 1966-1981. Our analysis shows that husband's age is *not* a surrogate for wife's age, in spite of its common use as such by Dr Hirayama. Since age at entry is confounded with cohort effects, it is also likely further that interactions occur between age and calendar period and between age and other covariates not represented in the model.

As a consequence of this finding, our conclusion is that the results of Hirayama's large study on ETS and lung cancer should *not* be pooled with other ETS/lung cancer studies to form a global estimate of relative risk. The relevance of this Japanese study's findings to public policy is questioned in the absence of more detailed information on exposure and follow-up, and more extensive analysis of the data at the level of the individual subject.

REFERENCES

1. Kilpatrick,S.J. (in press) Model specific effects in ETS/nutrition research.

   Int. Archives of Occ. & Environ. Hlth.

2. Hirayama,T. (1984) *Lung cancer in Japan: Effects of nutrition and passive smoking.*

   Chapter 14 of *Lung Cancer: Causes and Prevention* pp.175–196 Mizell,N. & Correa,P. (eds.) Verlag Chemie International 1984.

3. Breslow,N.E. & Day,N.E. (1986) *Statistical methods in cancer research. Volume 2. The design and analysis of cohort studies.*

   I.A.R.C. Scientific publications Number 82. Lyon, France.

4. Breslow,N.E. & Day,N.E. (1980) *Statistical methods in cancer research. Volume 1. The analysis of case-control studies.*

   I.A.R.C. Scientific publications Number 32. Lyon, France.

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Present and future of indoor air quality.
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AN EXAMPLE OF EXTRA-POISSON VARIATION SUGGESTING AN UNDER-SPECIFIED MODEL.

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INTRODUCTION

There is now an extensive literature on environmental tobacco smoke (ETS). Several meta-analyses of this literature have combined risk estimates for lung cancer from different studies weighted by the quality and size of the study. Thus, in their meta-analysis, Letzel et al. (1988) give various scenarios which use different figures from Hirayama's study, depending on whether the husband's or wife's age was used to adjust the wife's cumulative mortality. Since Hirayama's study constitutes about 20% of all lung cancer deaths in the ETS literature, it is important to use the correct relative risk from Hirayama in constructing global estimates. Here, it is shown that a proper analysis of Hirayama's study leads to a non-significant association between ETS and the risk of death from lung cancer in non-smoking wives.

Hirayama (1981) reports an age standardised risk ratio of 1.90 for lung cancer among non-smoking women married to heavy smokers and finds a highly significant trend ($P < 0.001$) between the amount smoked by husbands and the lung cancer mortality of their non-smoking wives. He also interprets this association as arising from a causal relationship between husband's smoking and wife's lung cancer:

> These results indicate the possible importance of passive or indirect smoking as one of the causal factors of lung cancer.
> (Hirayama, 1981)

THE STUDY

Dr. Hirayama's study links deaths from all causes occurring in the period 1966 -1981 to a questionnaire given in late 1965 to approximately 250,000 Japanese adults. Almost all those over age 40 in 29 Health Center Districts in 6 Japanese prefectures who were 'generally healthy' (Hirayama, 1978) were interviewed. At that time, each respondent was asked for his or her current smoking status. Although not originally designed as a study of the association between passive smoking and health, Dr. Hirayama subsequently linked the mortality of wives who were classified as non-smokers with their husband's smoking status and, if he was a smoker, with the amount smoked.

Hirayama's smoking classification is based on only one question at the time of the survey as to whether the respondent smoked, and, if so, smoked daily. The respondent was also asked whether he/she smoked occasionally, was an exsmoker, a non-smoker or an 'obscure' smoker. The age at which smoking started was recorded where appropriate. Husband's smoking status in 1965 was treated as an index of wife's ETS exposure. No direct measure of ETS exposure was made. In the following, ETS refers to this surrogate for passive smoking, i.e. the self-reported classification of a husband's smoking in 1965 when his wife was reported to be a

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non-smoker. In Hirayama's 1981 paper there was some ambiguity as to how he had treated the data. The estimates made by Hirayama of the association of ETS and lung cancer lead him to conclude:

> The relation between the husband's smoking and the wife's risk of developing lung cancer showed a similar pattern when analysed by age and occupation of the husband. (Hirayama 1981)

In response to his 1981 paper, a number of methodological questions were raised. In particular, Hirayama's use of the husband's age to adjust the wife's mortality was questioned.

> It is also not clear ... whether you standardised on the age of the wives themselves. Such calculations ... would certainly make the analysis more conclusive. (Harris & Du Mouchel, 1981)

Some years later, Hirayama responded to this criticism by analysing the wife's lung cancer mortality adjusted by the wife's age. In Hirayama (1984) the relative risk of 1.9, reported earlier, for non-smoking wives married to 'heavy' cigarette smokers drops to 1.7 when adjusted by wife's age. He concludes:

> There was a statistically significant increased risk [of lung cancer among non-smoking wives] in relation to the extent of the husband's smoking ... the association was significant when observed by age of husbands (table 1) and also by age of wives (table 2). (Hirayama, 1984 p.179)

THE DATA

Hirayama (1984) gives the lung cancer death rates in the period 1966-1981 for 91,540 self-reported non-smoking wives cross-classified by husband's smoking and by husband's age (Table 1) or wife's age (Table 2). In both tables, age is given in four 10 year age groups. Table 1 gives husband's smoking classified into 5 levels by the amount smoked daily.

TABLE 1

LUNG CANCER DEATH RATES per 1000 (1966-1981)
from Hirayama (1984)

		HUSBAND'S SMOKING				
		Non	Ex	1 – 14/*d*	15 – 19/*d*	20 + /*d*
HUSBAND'S AGE	40–49	0.6	0.8	0.9	1.2	1.5
	50–59	1.3	1.6	2.1	2.0	2.4
	60–69	2.5	4.1	3.9	3.6	4.9
	70–79	6.6	5.7	3.3	9.5	4.4

In order to make direct comparisons between the effect of adjusting by husband's or wife's age, Table 1 is collapsed to Table 1A, using the same grouping for husband's smoking as in Table 2, here called Non, Light and Heavy.

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TABLE 1A

LUNG CANCER DEATH RATES per 1000 (1966-1981) AND SAMPLE SIZE n (000) adapted from Hirayama (1984) Table 1

Husband's	Husband's smoking					
	Non		Light		Heavy	
Age	Rate	n	Rate	n	Rate	n
40-49	0.6	6.2	1.0	15.0	1.5	10.8
50-59	1.3	7.8	2.0	15.6	2.4	9.8
60-69	2.5	7.1	3.9	12.4	4.9	4.7
70-79	6.6	0.8	4.7	1.1	4.4	0.2

TABLE 2

LUNG CANCER DEATH RATES per 1000 (1966-1981) AND SAMPLE SIZE n (000) from Hirayama (1984)

Wife's	Husband's smoking					
	Non		Light		Heavy	
Age	Rate	n	Rate	n	Rate	n
40-49	0.5	7.9	1.2	17.5	1.7	12.6
50-59	1.8	7.6	2.9	15.6	3.5	8.8
60-69	2.6	6.2	3.0	10.4	2.6	3.8
70-79	17.4	0.2	1.5	0.7	8.4	0.2

Note that, in this paper, Table 1A and Table 2 of Hirayama (1984) are both 4 by 3 contingency tables, based on the mortality experience of the same 91,540 women.

MODELLING

The analysis of Table 1A and 2 is usually done using a fixed effects loglinear or logistic model (Breslow & Day 1986). These in turn are viewed as particular examples of a generalized linear model which may be misspecified in three ways

- the linear predictor may be incomplete or incorrect and or
- the wrong link may be used and/or
- the wrong error structure may be assumed.

In epidemiological investigations, the linear predictor is often incomplete in that important covariates are omitted or measured from the wrong origin or in the wrong scale. Such is likely to be the case here in that no allowance is made for diet, for cohort or period effects or for the duration and amount of ETS exposure, either before or after 1965.

As its name implies the loglinear model uses a linear predictor to fit the logarithm of the cumulative mortality rates. Here it is shown that a model allowing for extra-Poisson variation is necessary and that this model leads to a non-significant effect for ETS in Table 2.

The usual regression model relating interval or measurable quantities such as height and weight, assumes a normal distribution of errors about the regression line. By contrast, the loglinear model assumes a Poisson distribution of errors between the observed and fitted

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log(rates). The Poisson distribution, in turn, implies that the mean of the distribution equals the variance or dispersion of the distribution. In other words, the usual model for mortality rates estimates only the mean. Recently, this assumption has been called into question.

> Techniques like regression analysis ... have traditionally focussed attention on modelling and analysis of means or location parameters. Scale parameters have been regarded as nuisance parameters; interest in them has been largely limited to testing the equality of variances so that techniques that assume variance homogeneity can be applied. Recently, however, there has been more interest among statisticians in the structural modelling of variances and in the estimation of dispersion effects. (Anon., the American Statistical Association, 1988)

In the same year in which Hirayama published his only tabulation in which wife's age is used (Table 2 of Hirayama, 1984), Breslow (1984) published a method by which an extra term σ^2 could be added to the loglinear model to allow for excess variation beyond that assumed by a fixed effects model. The model for extra-Poisson variation is shown below to be an extension of the loglinear model.

If d_i deaths are observed among n_i wives, such that $E(d_i) = n_i\lambda_i$ for different subgroups i, then the loglinear model assumes that d_i follows a Poisson distribution with mean $n_i\lambda_i$, where d_i is related to a linear predictor via a logarithmic link or transformation

$E[ln(d_i/n_i)] = x_i\beta.$

In contrast, the extra-Poisson variation model assumes that

$E(d_i) = \mu_i \approx exp[ln(n_i) + x_i\beta]$

where β is a column vector of unknown regression parameters and where

$var(d_i) \approx \mu_i + \sigma^2\mu_i^2.$

The extra-Poisson variance, σ^2, is determined by an iterative re-weighting technique (Breslow 1984). Note that if there is no over-dispersion, σ^2 is estimated as zero.

RESULTS

The usual loglinear model fits Table 1A better than Table 2. Conventionally, a good fit is one for which the residual deviance is less than the degrees of freedom remaining after fitting the linear predictor. The residual deviance after fitting the same linear predictor, age plus husband's smoking level, is 2.0 in Table 1A and 10.7 in Table 2. Since Table 1A has been configured to have the same dimensions as Table 2, both of these deviances may be evaluated against 6, the number of degrees of freedom which remain after fitting age and husband's smoking. In summary then, the deviance for Table 1A is 2.0 with 6 d.f. as compared with a deviance of 10.7 with 6 d.f. for Table 2.

This is paradoxical. Why should the use of the wife's age give a worse fit than the husband's age when modelling the wife's lung cancer mortality? Since this is contrary to our expectation, it suggests that the model is incorrect in one or more of the three categories listed above: incorrect linear predictor, link or error structure.

To allow for the possibility of over-dispersion, Table 1A and Table 2 have been analyzed using the extra-Poisson loglinear model. σ^2 is estimated as zero in Table 1A and as 0.23 in Table 2. An approximate test for the significance of this estimated over-dispersion is to compare the square root of the reduction in deviance after fitting σ^2 with a one-sided Normal distribution. Such a test has an associated probability of 0.015. There is thus some support for the use of this model (and its conclusions) in preference to the fixed effects model. Moreover,

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It is not necessary that σ be significant in order to stay in the model. Often the data are suggestive a priori of excess variation and a prudent analysis will account for it even if not significant. (Mauritsen, 1988)

TABLE 3

EFFECT OF MODEL CHOICE ON P VALUES FOR ETS AS A FACTOR OR A TREND

MODEL	LOGLINEAR	EXTRA-POISSON
FACTOR	.01	.01
TABLE 1A		
TREND	.003	.003
FACTOR	.05	.63
TABLE 2		
TREND	.02	.37

Table 3 shows that this change of model has no effect in Table 1 in which husband's age is used. ETS is statistically significant, both as a factor ($P = 0.01$) and as a trend ($P = .003$) in Table 1A. Nevertheless, the change of model has a marked effect in Table 2 in which the wife's age is used. The ETS factor in Table 2 which is barely significant ($P = 0.05$) under the loglinear model is clearly not significant under the extra-Poisson model ($P = 0.63$). It is inappropriate to test for a trend before the factor has been shown to be significant, in the absence of a prior hypothesis for trend. However, here, following Dr. Hirayama, the trend of the relative risk against the level of ETS is tested. The ETS trend of log (relative risks) with husband's smoking (non, light and heavy) which was just significant ($P = 0.02$) is now, under the model for extra-Poisson variation, not a significant trend ($P = 0.37$).

TABLE 4

EFFECT OF MODEL CHOICE ON 95% CONFIDENCE LEVELS FOR ETS RELATIVE RISKS

MODEL	LOGLINEAR	EXTRA-POISSON
LIGHT	0.98-2.08	0.98-2.08
TABLE 1A		
HEAVY	1.24-2.81	1.24-2.81
LIGHT	0.92-1.97	0.49-2.51
TABLE 2		
HEAVY	1.10-2.48	0.64-3.41

An alternative way of showing the effect of making the model more general is to display the 95% confidence limits for specific levels of ETS exposure. As is seen in Table 4, the model choice has no effect on 95% confidence limits in Table 1A, being 0.98 – 2.08 for the Light vs Non relative risk and 1.24 – 2.81 for the Heavy vs Non relative risk. The choice of model however does affect the 95% confidence limits in Table 2. Here, the Light vs Non relative risk changes from 0.92 – 1.97 to 0.49 – 2.51, neither of which are statistically significant, since both contain the non-effect level of 1.0. The Heavy vs Non relative risk in Table 2 changes from 1.10 – 2.48 to 0.64 – 3.41, so that the interpretation of this association also changes from statistically significant to nonsignificam. Thus, even when the husband reports smoking 20– cigarettes daily, the non-smoking wife shows no significantly increased risk from passive smoking.

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TABLE 5

EFFECT OF MODEL CHOICE ON 95% CONFIDENCE LIMITS FOR ESTIMATES OF ETS TRENDS

MODEL		LOGLINEAR	EXTRA-POISSON
TABLE 1A	TREND	1.11-1.66	1.11-1.66
TABLE 2	TREND	1.05-1.56	0.80-1.87

As shown in Table 5, the 95% confidence limits are consistent with the P values for trend given above. No change is observed in the 95% confidence limits, 1.11 – 1.66, for the trend relative risk in Table 1A. The previously significant trend in Table 2, with 95% confidence limits of 1.05 – 1.56, becomes non-significant with limits of 0.80 – 1.87.

DISCUSSION

Hirayama's analysis assumes that the risk of a lung cancer death is constant within each of the twelve age/exposure sub-groups of Table 2 over the period 1966-1981 and yet:

> Environmental variables are ... difficult to quantify since individual histories vary widely with respect to the onset, duration and intensity of exposure and whether it was continuous or intermittent. (Breslow & Day 1980)

Unfortunately, the danger of using a fixed effects model when unwarranted is that the error term is underestimated.

> Tests of significance and confidence intervals that fail to account for the lack of fit of a given model may be seriously misleading. (Breslow 1987)

Such is the case here. Dr. Hirayama's use of a fixed effects model which gives a poor fit has resulted in his reporting a spuriously significant result. Fitting a more general model confirms that extra-Poisson variation is present in Table 2 (where the wife's age is used) though not in Table 1A (where the husband's age is used instead).

The finding of excess dispersion in this longitudinal record linkage study is likely to be due to the omission of period and cohort effects from the model. Osmond & Gardner (1989) have shown that

> When the assumptions [in the model] are inappropriate, as is usually the case, misleading results will occur.

The period 1966-1981 saw an increasing use of cigarettes in Japan (Kristen 1986) and an increasing mortality from lung cancer in women so that it is unlikely that the association between ETS and lung cancer remained constant over this 16 year period, as is assumed in Hirayama's analysis.

The non-independence of observations within subgroups effectively reduces the sample size, increases the variance and widens the 95% confidence limits for the relative risk of ETS. This is illustrated by the fit of a model allowing extra-Poisson variation, since now the 95% confidence limits include 1.0. In other words, with this model, ETS is no longer significantly associated with lung cancer mortality in non-smoking wives.

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No change is observed, however, after fitting the more general model to Table 1A. ETS is still significantly associated with female lung cancer mortality. This is interpreted as being due to the substitution of husband's age for wife's age. Thus, while the linear predictor used in Table 2 (Wife's Age – Husband's Smoking) demonstrates the absence of period and cohort terms through the need to estimate an extra-Poisson variance component, the linear predictor used in Table 1A (Husband's Age – Husband's Smoking) does not. Rather a model which uses Husband's Age is seen as mimicking a model which includes
(Wife's Age + Husband's Smoking + Wife's Cohort + Period Effects).

Recent research supports this interpretation. Logue & Wing (1986) show that record linkage studies which use rates cumulated over 20 years can produce just the effect reported here, an age/exposure interaction. Under these circumstances, the significance of ETS in Table 1A should *not* be interpreted as indicating a causal relationship but simply that the husband's age, together with husband's smoking status, are proxies for other important but unnamed determinants of an observational study over time.

SUMMARY and CONCLUSIONS

If the wife's mortality from lung cancer is adjusted by the husband's age, the loglinear model gives a good fit and husband's smoking has a significant association with lung cancer mortality in non-smoking wives. It is, however, better to adjust by a person's own age. A consequence of using the wife's age to adjust the wife's mortality from lung cancer is that a loglinear model with extra-Poisson variation is required. With this model, the risk factor, 'husband's smoking', is not statistically significant, indicating no increased risk of lung cancer mortality in non-smoking wives of smoking husbands.

Because of this finding, it is important to use the correct analysis of Hirayama's study in future meta-analyses of published ETS studies in order to get a global estimate of the association of spousal smoking with lung cancer death rates in non-smokers. Such an analysis should incorporate the wife's age when the wife's lung cancer mortality is analyzed.

REFERENCES

- Anon (1988) Amstat News July-August 147, 1
- Breslow NE (1984) J Roy Stat Soc. C 33, 1. 38-43
- Breslow NE (1987) German-American Seminar on Longitudinal Studies and their Analyses. Inst for Social Med
- Breslow NE & Day NE (1980) Statistical Methods in Cancer Research
  Vol I- The Analysis of Case-Control Studies
  I A R C Sc Pub No 32
- Breslow NE & Day NE (1986) Statistical Methods in Cancer Research
  Vol II- The Design and Analysis of Cohort Studies
  I A R C Sc Pub No 82

2023381549

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

- Harris, JE & Du Mouchel WH (1981) Br Med J 283, 915-916, 3 Oct
- Hirayama T (1978) Nutrition & Cancer 1, 3, 67-81
- Hirayama T (1981) Br Med J 282, 183-185, Jan 17
- Hirayama T (1984) In: Mizell M & Correa P (eds) Lung Cancer: Causes and Prevention Verlag Chemie Int p 175-195 Ch 14
- Kristen MM (1986) Int J Epidemiology 15, 1, 140-141
- Letzel H, Blümner F & Überla K (1988) In: Indoor & Ambient Air Quality, Perry R & Kirk PW (eds) Selper, London pp 293-302
- Logue EE & Wing SJ (1986) Chron Dis 39, 709-717
- Mauritsen R (1988) EGRET Users' Manual Part 3 p 77 S E R C Seattle, Wash
- Osmond C & Gardner MJ (1989) Am J Epidemiology 129, 31-35

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Model Specification Effects in ETS/Nutrition Research

S. J. Kilpatrick

Summary

In Hirayama's study the average annual death rate for wives aged 60–69 from lung cancer is 18 per 100,000 as compared with 39 for all Japanese women (Exhibit 9). Also, wives aged 50–59 have the same lung cancer death rate as wives aged 60–69 (i.e., no age trend). These results may arise from the 23% of the cohort which is missing.

These anomalies are obscured in Hirayama (1984) by the use, in all but one table (Table 2), of husband's age rather than the wife's age.

Using wife's age to analyze wife's mortality leads to an additive model for lung cancer. The use of the relative risk is thus contra-indicated.

The weak association of husband's smoking status with wife's lung cancer mortality is probably a consequence of incomplete age adjustment when coarse age groups of 10 years are used over a 16-year period. Suggestions are made for further analyses using ungrouped information.

The effect of daily intake of green and yellow vegetables on lung cancer is also reanalyzed. A standard analysis of these data leads to different results than those given by Hirayama (1984).

Public examination of these data is called for to yield independent answers to the questions raised here.

Introduction

Hirayama (1984) reports on a longitudinal record linkage study of married women who, in 1965, were reported to be non-smokers. Interviews using form 1 (see Exhibit 1) were carried out October through December 1965 of persons 40 years and above in 49 districts in 29 health center districts in Japan. In 1971, a 3% sample of those subjects were re-interviewed (Hirayama 1982) using form 2 (Exhibit 2). Form 2 is form 1 with additional questions on current health status and illnesses in the past five years. A second follow up was apparently done between 1971 and 1983 since Hirayama (1984) refers to a recent study of 410 males and 158 females in Aichi province. Apart from these, no monitoring of the population was carried out apart from linking deaths in the period 1966 to 1981 to the original questionnaire (Exhibit 1).

The cause of death in those women who had died by 1981 was linked to the initial interview in 1965 of both husband and wife. In the sequel it is important to note that date of birth, age of first marriage, age started smoking and date of death are recorded. Linkage of a married couple's original responses to the wife's death certificate can therefore yield the woman's precise age at entry. Likewise, for a non-smoking wife, the

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Exhibit 1

Form 1 Initial survey

Health Questionnaire Name of Prefecture Health Center

District code	Household code	Individual code
Name	M / F	Date of birth (year month day) 1. Single 2. Married 3. Divorced 4. Widowed
Address		
Place of birth: Prefecture	City	Occupation (in detail)
For women: Number of children	Length of breast feeding after last delivery month(s)	Age at first marriage

Anamnesis

Eating Habits	Rice/Wheat	Amount/day Frequency
	Meat	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Fish and shell fish	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Milk and goat milk	1. Daily(amount) 2. Occas 3. Rare 4. None 5. Obscure
	Green-yellow vegetables	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Pickles	1. Every meal 2. Daily 3. Occas 4. Rare 5. None 6. Obscure
	Soybean paste soup	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
Favorites	Smoking	1. Smoking daily (a) Cigarette No./day (b) Kiseru (c) Others 2. Occas 3. Ex. 4. None 5. Obscure Age started ( )
	Alcohol	1. Daily 2. Occas 3. Rare 4. None 5. Obscure Type (1) Sake (2) Shochu (3) Beer (4) Whisky (5) Others (6) Obscure
	Green tea	1. Very hot 2. Moderate 3. None 4. Obscure

age at which the husband started smoking and the date of the marriage can yield the duration of exposure to husband's cigarette smoke at the first interview.

The data from this study as presented by Hirayama (1984) has been summarized in 10 tables for non-smoking wives. Exhibit 3 lists these tables and shows by table number the cause of death and the factors by which the cause of specific death rates are classified. The levels of a given factor are given in parentheses. Note that Table 5 is a collapsed form of Table 6 or of Table 10 and Table 7(1) of Table 7(2). Note that Table 9 is Table 8 omitting non-smoking husbands. Only one Table, Table 2, gives wife's age group. The relationship of wife's age group to her daily intake of green/yellow vegetables is not given, nor of wife's age group to husband's age group, husband's drinking habit or husband's occupational group.

Poisson Regression

The following gives the standard analysis of the tables published in Hirayama (1984). Since Tables 5, 7(1) and 9 are all collapsed versions of other Tables, they are omitted from

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Exhibit 2

Form 2 **Second survey**

Health Questionnaire Name of Prefecture Health Center

District code	Household code		Individual code
Name	M / F	Date of birth (year month day) 1. Single 2. Married 3. Divorced 4. Widowed	
Address			
Place of birth	Prefecture	City	Occupation (in detail)
For women	Number of children	Length of breast feeding after last delivery month(s)	Age at first marriage

Anamnesis

Eating Habits	Rice/Wheat	Amount/day Frequency
	Meat	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Fish and shell fish	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Milk and goat milk	1. Daily(amount) 2. Occas 3. Rare 4. None 5. Obscure
	Green-yellow vegetables	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Pickles	1. Every meal 2. Daily 3. Occas 4. Rare 5. None 6. Obscure
	Soybean paste soup	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
Favorites	Smoking	1. Smoking daily (a) Cigarette No./day (b) Kisami (c) Others 2. Occas 3. Ex. 4. None 5. Obscure Age started ( )
	Alcohol	1. Daily 2 Occas 3. Rare 4. None 5. Obscure Type (1) Sake (2) Shochu (3) Beer (4) Whisky (5) Others (6) Obscure
	Green tea	1. Very hot 2. Moderate 3. None 4. Obscure Others (1. Tea 2. Coffee 3. Cola 4. Cider)
Current Health Status (danger signals)		1. Stomach trouble, indigestion, no appetite, change in food choice. 2. Vaginal discharge, irregular bleeding. 3. Lump in the breast 4. Difficulty in swallowing. 5. Blood or mucos in stool. 6. Continued cough, bloody sputum, hoarseness. 7. Chronic ulcer in the mouth/skin. 8. Difficulty in urination, blood in urin. 9. Irritation/uneasiness 10. Difficulty in sleeping. 11. Heart trouble.
Currently		1. Healthy 2 In bed (by) from when.
Major illness during past 5 years		name of illness time duration. 1) 2)
Health Check		1 none 2 yes (stomach X ray chest X ray blood pression others)

analysis. Note that, because of different groupings of husband's occupational group, Table 3 cannot be derived from Table 8, nor Table 6 from Table 10. Indeed, since person years are not given, the study appears to call for a Proportional Mortality Analysis of lung cancer, other cancer and ischemic heart disease mortality in non-smoking wives, cross-classified by wife's age group (4) × husband's age group (4) × husband's smoking classification (5) × husband's drinking habit (4) × husband's occupational group (10) ×

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Exhibit 3

Tables as presented in Hirayama(1984)

TABLE	OUTCOME	FACTORS*
1	LCD	HAGE(4) x HCIG(5)
2	LCD[1]	WAGE(4) x HCIG(3)
3	LCD	HAGE(4) x HCIG(3) x HOCC(10)
4	LCD	HAGE(4) x HALC(4)
5	IHD[2]	HAGE(4) x HCIG(3)
6	IHD	HAGE(4) x HCIG(3) x HOCC(10)
7(1)	OTHCA[3]	HAGE(4) x HCIG(3)
7(2)	OTHCA	HAGE(4) x HCIG(3) x HOCC(10)
8	LCD	HAGE(4) x HCIG(3) x HOCC(2) x GYV(2)
9	LCD	HAGE(4) x HCIG(2) x HOCC(2) x GYV(2)
10	IHD	HAGE(4) x HCIG(3) x HOCC(2) x GYV(2)

1 LCD.....lung cancer deaths

2 heart disease deaths

3 cancer deaths

*Factors:

HAGE husband's age group

WAGE wife's age group

HCIG husband's daily smoking habit

HALC husband's daily alcohol intake

HOCC husband's occupational group

GYV wife's daily intake of green & yellow vegetables

Levels: In a factor XXX(n), n is the number of levels of factor XXX in the specified table

wife's daily intake of green/yellow vegetables (2). Parenthetically there is no reason today why, with modern computing techniques this basic tabulation should not have been analysed directly, instead of piecemeal as reported. Unfortunately the basic data is not available to the author (Hirayama, personal communication).

The analysis which follows is that recommended by Breslow & Day (1986) for cohort studies. In the absence of person years, the cumulative mortality rate over the period 1966–1981 is used as the response variate. (This assumes no "competing" causes of death and no loss to follow-up. This rate is not strictly a risk estimate since it depends on the duration of the study, the period of the study and on the choice of study population). A Poisson error structure is specified with a logarithmic link function which is the default for a Poisson error structure in GLIM (Payne 1985). The regressions are weighted according to the number of non-smoking wives in each cell.

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Following Breslow (1987), nuisance variables, irrespective of their technical significance, are fitted before the factor of interest, i.e. either husband's smoking status or green and yellow vegetable intake. A factor is considered to have a significant association with the specified mortality rate only if the deviance reduction in the model, for the degrees of freedom associated with fitting that factor, is significant at the 5% level. (Note that Dr. Hirayama here uses a one-sided 10% level of significance which is equivalent to a two sided test at 20% significance). Analysis of residuals and regression diagnostics are not given here. Rather the model fit is evaluated using the approximation of the residual deviance and its degrees of freedom to the χ^2 distribution which "may overstate the degree of departure from the fitted model when many cells contain small counts" (Breslow & Day 1986, p. 137).

Husband's Age Group, Husband's Drinking Habit and Lung Cancer Mortality

Age at interview is clearly a powerful factor which must be fitted first. In some tables age exhibits a powerful linear trend and can be fitted as a single numeric variable. Where this is possible it is done to achieve the most parsimonious model.

Table 4 gives a cross classification of husband's age group × husband's drinking habit for lung cancer mortality in non-smoking wives. It is surprising that other "nuisance factors" are not included. Nevertheless, this table is analysed first, largely to investigate the association of lung cancer mortality with husband's age group.

Standard Poisson regression of Table 4 confirms that husband's age group is an important factor in lung cancer mortality (see Exhibit 4). Husband's age group exhibits a strong linear trend with lung cancer mortality. A log-log plot of lung cancer mortality rate vs husband's age group however gives a slope less than 3 whereas a slope of 4 has been reported for non-smokers using attained age (Seidman 1985). Husband's drinking habit shows no significant association in this table with lung cancer mortality but no adjustment has been made for other nuisance variables. Thus one would expect an association between husband's drinking and smoking habits.

ETS and Lung Cancer Mortality (Tables 1, 2, 3)

The only measure of ETS exposure given is husband's smoking classification, the number of cigarettes reported in 1965 as smoked daily by the husband. The standard practice of demonstrating that a factor is significant before looking for a trend is followed here. As for husband's age group in Table 4 above, husband's smoking classification shows a strong linear trend in certain tables and is entered as a single numeric variable in the interests of parsimony where possible.

"Typical practice is to consider 5 year intervals of age and time so as to be able to study variation in rates" (Breslow & Day 1980, p. 47–48). Hirayama (1984) uses 10 year age groups and does not divide the 16 year period. In general, an age classification of 10 years at entry in a study lasting 16 years with no time dependent factors may mean that the age effect has been incompletely adjusted (Mantel 1983). Thus, for a lung cancer mortality rate which rises exponentially with age, it is plausible that the significance of husband's smoking classification is an indication of incomplete age adjustment, given the rapidly changing habits of cigarette smoking in the period before 1966 (Kristen 1986).

Note also that duration of ETS exposure is confounded to an unknown extent with age at first interview. Thus, in the absence of other information, assume a constant age at

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Exhibit 4

Summary of the fit of the best† multiplicative model

OUTCOME TABLE	PREDICTIVE MODEL	DEVIANCE(d.f.)
LCD 1	A	13.0 (18)
	A+HCIG	3.7 (14)
LCD 2	WAGE	16.8 (8)
	WAGE+HCIG	10.7 (6)
LCD 3	A+HOCC+C	71.9 (108)
LCD 4	A	15.3 (14)
IHD 6	HAGE+HOCC	115.1 (106)
	HAGE+HOCC+HCIG	109.6 (104)
OTHCA 7(2)	HAGE+HOCC	134.7 (106)
LCD 8	A+HOCC+C	50.8 (44)
IHD 10	HAGE+HOCC+HCIG	50.7 (41)

Key:

A is husband's age fitted as a linear trend

C is husband's daily smoking habit fitted as a linear trend

other factors, outcomes as defined in Exhibit 3

†Best in the sense of minimum residual deviance after fitting all 'nuisance' parameters as factors or (if warranted) as trends and then fitting the explanatory variables, HCIG [Tables 1, 2, 3, 4, 7(1)] or GYV [Tables 8, 10].

marriage and at starting smoking. In 1965, older non-smoking wives of smoking husbands will have been exposed to ETS for a longer period than younger wives. (This expectation of an increased relative risk for older wives is not evident from an analysis of Table 2 (see Exhibit 7)). Form 1 (Exhibit 1) records the age at which the husband started smoking. Given this and the date of the marriage from a linked wedding certificate, it should be possible to estimate the duration of ETS exposure by the non-smoking wife of a smoking husband prior to 1966 as well as the wife's age at first exposure.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 1, like Table 4, gives the cross-classification of husband's age group × husband's smoking status. As shown in Exhibit 4, only husband's age group is significant and exhibits a strong trend, as in Table 4. Although husband's smoking classification is not significant, it approaches significance ($\chi^2 = 9.3$ on 4 degrees of freedom, P just greater than 5%).

The effect of re-classifying husband's smoking classification from 5 levels to 3 levels can be seen in Table 3 which also gives a breakdown by 10 occupational groups, HOCC (10). Although husband's occupational group with 9 degrees of freedom is not significant, husband's smoking classification with 3 levels now is. Indeed husband's smoking classification with three levels now exhibits a strong trend (Exhibit 4).

Table 2 is unique in this publication in that lung cancer mortality is adjusted for wife's age group. Indeed this appears to be the only occasion on which Hirayama has included wife's age group in an analysis in any of his many publications from this study. (We shall see that husband's age group is not a surrogate for wife's age group.)

Standard Poisson regression of Table 2 as presented shows (Exhibit 4) that wife's age group, while a significant factor, does not exhibit a trend against lung cancer mortality. Again husband's smoking classification is on the borderline of statistical significance as judged by the change in the deviance ($\chi^2 = 6.1$ on 2 degrees of freedom). Clearly the evidence for a significant relationship between lung cancer mortality and husband's smoking classification is ambivalent even without considering the influence of non-sampling errors and confounding factors.

ETS and Ischemic Heart Disease (Tables 5, 6)

The consideration of multiple outcomes for associations with ETS indicates the multivariate nature of the analysis and the lack of prior hypotheses in this study. One should allow for multiple or repeated tests of significance in the evaluation of these results.

Table 6 gives a tabulation of ischemic heart disease mortality by husband's age group, husband's smoking classification and husband's occupational group. After adjustments for both husband's age group and husband's occupational group are made (Exhibit 4), husband's smoking classification is just non-significant by the established criteria ($\chi^2 = 5.6$ on 2 degrees of freedom). This is in contrast to Table 5 (not shown) which is Table 6 collapsed over husband's occupational group, showing some confounding between husband's occupational group and husband's smoking classification for ischemic heart disease.

ETS and Other Cancers

Table 7 (2) classifies other cancer against husband's age group, husband's smoking classification and husband's occupational group, the same classification as for lung cancer mortality (Table 3) and for ischemic heart disease (Table 6). This again points out that a Proportional Mortality Analysis is the preferred method of analysis here. A univariate log linear analysis confirms that husband's occupational group is significantly associated with other cancer mortality. This association is almost entirely due to husband's occupational group 5, "farmers, laborers and fishermen" which has an estimated relative risk of 1.45 with 95% confidence limits of (1.04–2.03). No significant association with husband's smoking classification is detected with other cancer.

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Green/Yellow Vegetables and Lung Cancer Mortality (Table 8)

Switching the focus now from husband's smoking classification to daily intake of green/yellow vegetables, we first fit all factors other than daily intake of green/yellow vegetables in Table 8 as nuisance parameters. The analysis of deviance reduction establishes that daily intake of green/yellow vegetables has a non-significant association (Exhibit 4).

Green/Yellow Vegetables and Ischemic Heart Disease (Table 10)

Table 10 gives ischemic heart disease mortality by husband's age group, husband's smoking classification, husband's occupational group and daily intake of green/yellow vegetables.

No significant association is found (Exhibit 4) with daily intake of green/yellow vegetables, after adjustment for these other factors ($\chi^2 = 0.6$ on 1 degrees of freedom).

In summary, standard Poisson regression, using the conventional 5% level of significance indicate, on the basis of these published tables,

- husband's smoking classification is marginally associated with wife's lung cancer mortality, the size of the effect being of borderline significance and dependent on the presence or absence of other factors in the model and the number and grouping of classes used in the husband's smoking factor.
- that husband's drinking habit shows no significant association with lung cancer mortality in the limited data published here.
- that daily intake of green/yellow vegetables shows no significant association with lung cancer mortality or with ischemic heart disease mortality.
- that husband's smoking classification is of borderline significance with wife's ischemic heart disease mortality.
- that husband's smoking classification shows no significant association with other cancer mortality.

These findings may be compared against those of the original report. There Hirayama (1984) claims "a significantly increased risk of" lung cancer mortality "in relation to the extent of the husband's smoking... The association was significant when observed by age of husbands... and also by age of wives." "Similar significant risk elevation of lung cancer with the increase in the extent of husband's smoking was observed with ischemic heart disease when observed by husband's age group and husband's occupational group."

"The risk-reducing effect of daily intake of green-yellow vegetables on lung cancer was observed for passive smoking... Those women eating green-yellow vegetables daily showed a significantly lower risk of lung cancer from the passive influence of their husbands' smoking."

Power Fit

Exhibit 4 which summarizes the best fitting multiplicative model indicates that in some instances this fit may not be too good (or that interaction terms are necessary). Thus, the residual deviance considered as an approximate χ^2 indicates that for both models fitted toTable 2, the fit is of borderline significance. This is true also of Table 7 (2), Table 8 and

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Exhibit 5

Deviances (df) for additive, multiplicative and best fitting power models

OUTCOME TABLE	MODEL ADDITIVE	POWER	MULTIPLICATIVE
LCD Table 1	3.79 (12)	2.76 (12)	3.24 (12)
LCD Table 2	7.91 (6)	7.85 (6)	10.72 (6)
LCD Table 3	2.57 (6)	1.50 (6)	1.95 (6)
IHD Table 5	2.32 (6)	2.17 (6)	2.72 (6)
OTHER CA Table 7(1)	3.28 (6)	2.46 (6)	3.68 (6)

Model is 1+HAGE(4)+HCIG(5) for Table 1
..... 1+WAGE(4)+HCIG(3) for Table 2 and
..... 1+HAGE(4)+HCIG(3) for Tables 3, 5 and 7(1)

Rates are DTHS/POP (1966-1981)
for LCD (Tables 1,2,3), OTHER CA (Table 7(1)), IHD (Table 5)

Table 3 has been collapsed over HOCC

Table 10. This test is approximate. Nevertheless, it was decided to investigate the best fitting power model (Breslow 1986) to these tables. The goodness of fit of the additive, multiplicative and best fitting power model to these data are compared in Exhibit 5 in terms of residual deviance. Note that the additive and multiplicative models are special cases of the power model with exponents equivalent to one and zero respectively.

In Exhibit 5, an attempt has been made to fit the same predictive equation, adjusting for age and ETS exposure across the different sets given in Hirayama (1984). Overall, husband's age in 1965 classified by 10 year age groups, gives very satisfactory fits, irrespective of which Poisson model is used. In contrast, Exhibit 5 shows that poor fits result from the use of wife's age in 1965, classified in 10 year age groups, the multiplicative model giving the worst fit.

Exhibit 5 also reveals that the power-deviance curve is generally quite flat. Apart from Table 2, for which the additive model is the model of choice, the data, as presented in Hirayama (1984), do not discriminate well between additive and multiplicative models.

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Exhibit 6

POWER VALUE FOR BEST MODEL

OUTCOME	POWER ρ	$\hat{\rho}$	ρ
LCD Table 1	1	0.40	0
LCD Table 2	1	1.14	0
LCD Table 3	1	0.39	0
IHD Table 5	1	0.61	0
OTHER CA Table 7(1)	1	-	0

predictive equations as in Exhibit 5

- $\hat{\rho}$ meaningless since HC1G has zero estimates

The power value in the best fitting model is given in Exhibit 6. This lies between $\rho = 1$, the additive model and $\rho = 0$ (which is equivalent to the multiplicative model) for all but Table 2. The best fitting power model for Table 2 is larger than 1.00, indicating that the multiplicative model as fitted above, is contra-indicated. An additive model, then, is clearly preferred over the multiplicative model for Table 2, which, alone, uses wife's age group. However, the flatness of the deviance curve against ρ may indicate that the assumption of a Poisson error term is incorrect.

This finding may be interpreted in biological terms and in terms of information content. Although this study is considered to be one of the largest on ETS and lung cancer and contributes heavily to any meta-analysis estimate of passive-smoking effect (NRC report. 1986) it contains little information because of the absence of specific exposure, person year and time dependent data.

Wife's Age (Table 2)

Having shown that the additive model is the model of choice for Table 2, we now consider this analysis more fully. Unfortunately we are restricted to this one simple cross classification of wife's age group by husband's smoking classification using coarse intervals and omitting others factors. Under the additive model, wife's age group and husband's smoking classification are significant factors ($\chi^2 = 32.6$ on 3 degrees of

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Exhibit 7

Table 2 Lung Cancer Relative Risk (1966–1981)

		HUSBAND'S SMOKING		
		Non	Ex or 1 – 19/d	20 + /d
WIFE'S AGE	40–49	1.0	2.4	3.3
	50–59	1.0	1.6	1.9
	60–69	1.0	1.2	1.0
	70–79	1.0	0.1	0.5

freedom for wife's age group and 8.84 on 2 degrees of freedom for husband's smoking classification, $0.05 > P > 0.01$).

Although this is an improvement over the multiplicative model, the residual deviance is 7.91 on 6 degrees of freedom, indicating that this model may still not be good fit. Likewise the best fitting power model had residual deviance of 7.85 on 6 degrees of freedom – not a great improvement.

This is paradoxical. As we move from husband's age group to wife's age group (which should give a more direct relationship between age and lung cancer mortality) we, in fact, find continued evidence of an interaction between wife's age group and husband's smoking classification, irrespective of which model we use. It must be concluded that Table 2 contains insufficient detail in wife's age group and exposure to ETS or that other factors, not shown, are associated with lung cancer mortality in the non-smoker.

An alternative way of explaining why the multiplicative model is not the model of choice when wife's age is used is to examine the relative risks. The use of the multiplicative model assumes that the relative risk is constant with age. Exhibit 7 however demonstrates a clear trend in the relative risk which falls from values above 1 at young ages to values below 1 over 70. These trends arise because of the different effects of age in the three smoking status categories. Clearly (as may be seen from Exhibit 8 (figure)) the rates for the three smoking status categories are approximately equal at wife's age 60–69 but differ (in different directions) at other ages. Exhibit 9 compares average annual rate by wife's age (Table 2) with the same rate when classified by husband's age (Table 1) and both are compared with estimated Japanese rates for females. The rates for Table 1 and Table 2 are both uniformly lower than Japanese rates for women. Either wives have a much more favorable experience than all women or Hirayama's study subjects are unrepresentative of Japanese wives or both. In addition Exhibit 9 reveals an anomaly in Table 2 in that, unlike Japan or Table 1, the lung cancer death rates when classified by wife's age show no age trend from age group 50–59 to 60–69!

This suggests a serious misclassification of wife's age, wives who were 50–59 being recorded as 60–69 at the initial interview. Alternatively, and more likely, lung cancer deaths for wives aged 60–69 at initial interview are seriously under reported, giving a spuriously low average annual year lung cancer death rate of 18 per 100,000 as compared with a Japanese rate for all women of 39.

Turning now to an examination of the selected cohort, we look at the percentage distribution of husband's smoking status by wife's age. Exhibit 10 gives a 1965 cross-

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Exhibit 8

Table 2 Wife's Lung Cancer Death Rate (logarithm) (1966–1981) by Husband's Smoking Status (1965)

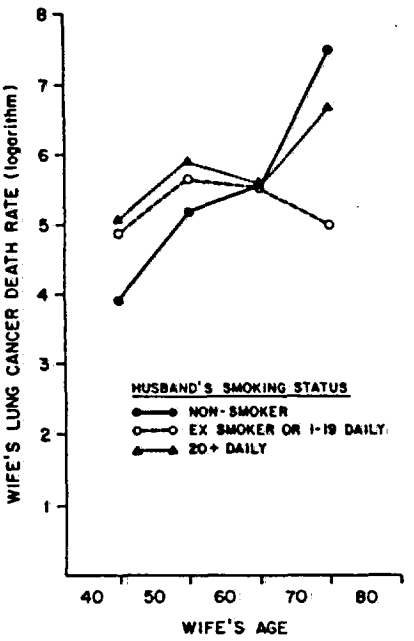

Exhibit 9

COMPARISON OF RATES BY AGE

Annual Average Lung Cancer Death Rate /100,000

1966–1981

AGE	JAPAN†	TABLE 1*	TABLE 2
40–49	12	7	8
50–59	20	12	18
60–69	39	23	18
70–79	46	36	35

† based on Japanese rates for women. (Segi et al., 1981)

* husband's age.

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Exhibit 10

Table 2 Distribution of Husband's smoking status by Wife's age

		HUSBAND'S SMOKING			
		Non	Ex or 1 – 19/d	20 + /d	Total
WIFE'S AGE	40–49	21%	46%	33%	38,025(100%)
	50–59	24%	49%	27%	32,089(100%)
	60–69	30%	51%	19%	20,344(100%)
	70–79	16%	62%	22%	1,082(100%)

Exhibit 11

Table 1 Distribution of husband's smoking status by his age

		HUSBAND'S SMOKING					
		Non	Ex	1 – 14/d	15 – 19/d	20 + /d	TOTAL
HIS AGE	40–49	19%	4%	27%	16%	34%	32,027(100%)
	50–59	23%	6%	29%	12%	30%	33,253(100%)
	60–69	29%	11%	30%	10%	19%	24,214(100%)
	70–79	37%	17%	30%	5%	11%	2,046(100%)

sectional view of cohort changes in husband's smoking habits. A number of points arise. Although Dr. Hirayama has published no information from his 3% re-interview survey on changes in smoking status between 1965 and 1971, such changes in smoking status occurred and may be of the order demonstrated in Exhibit 10 for husbands. (We have no information on wife's changes in smoking habits. Dr. Hirayama claims that 1.96% of the women polled in his 3% re-interview survey were misclassified as to smoking status. It is difficult to understand how he can discriminate between conversion from non-smoking to smoking status given the nature of the smoking question revealed in Exhibits 1 and 2. If 1.96% of wives were misclassified, what is the conversion rate from non-smokers to smokers in the period 1965–1971 among these wives?)

Secondly, the intermediate smoking classification (Ex or 1–19/d) is the most numerous of the three smoking status classifications for the husband and is a composite of ex-smokers and light and intermediate smokers (1–14/d and 15–19/d). It could be argued that as the most numerous the intermediate group should be used as the baseline for testing the significance above and below these rates for non-smokers and heavy smokers (20+/d) respectively. However, this group of wives has an unknown mixture of exposures to passive smoking. As indicated above, form 1 (see Exhibit 1) records

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information on duration of exposure of a wife to her husband's smoking but this has never been used in Dr. Hirayama's many publications.

Finally, a husband's smoking status is clearly dependent on his age (Exhibit 11). Thus, as a surviving husband ages he is less likely to be classified as a 20+/d smoker and most likely to be classified as a non-smoker or ex-smoker. Dr. Hirayama groups ex-smokers with light smokers (what happens to "occasional smokers"? (see form 1 (Exhibit 1)). In terms of exposure before 1966 this is correct but it may be argued that ex-smokers should be grouped with non-smokers since wife's exposure is zero after 1965 and lung cancer latency is of the order of 10 years.

Better still, fine detail should be preserved in order to allow for the true expression of factors and covariates. Thus it is likely that the association of husband's smoking status with wife's lung cancer mortality is simply an example of incomplete age adjustment, using 10 year age groups with a 16 year cumulative mortality. In other words, husband's smoking status is confounded with wife's age. Again this can be remedied by using modern analytical techniques to analyse the data in detail.

Discussion

Dr. Hirayama's publications, over the years, have analyzed this longitudinal record linkage study from many aspects. Given the nature of the study and the absence of specific details, it is clear that these data can not be used to confirm hypotheses or to strengthen the evidence for or against a causal mechanism between causes of death (his outcomes) and his factors, since "we can be easily misled by variables not represented or recognized in a study" (Tukey & Mosteller 1977, p. 119) and since "tests of significance and confidence intervals that fail to account for the lack of fit of a given model may be seriously misleading " (Breslow 1987, p. 37).

The absence of relevant factors and specific details is shown here in the inability of these published data to discriminate between additive and multiplicative Poisson regression models. It is unfortunate that the Committee on Passive Smoking (NRC 1986) gave so much weight to Dr. Hirayama's conclusions in their review of the evidence for and against passive smoking as a cause of lung cancer.

This standard re-analysis of Hirayama (1984) points to husband's smoking status being a surrogate for some other factor or factors. Thus, an unadjusted analysis of husband's alcohol intake showed no association with lung cancer mortality. If husband's smoking status were a causal factor in the formation of lung cancer, one would expect alcohol intake also to be associated with this risk because of the association of smoking and drinking habits.

Comparison with other cohort studies shows how approximate the evaluation of ETS exposure is in this study. Thus, for example, Smith & Doll (1982), investigating the effect of irradiation on leukemia mortality use both age at first exposure and duration since first exposure as factors. Dr. Hirayama has linked his initial interview file with death certificates for selected causes of death. It should be possible to link wedding, divorce and death certificates (for all causes) to the original file in order to estimate the duration of the marriage. Further, since the age at which the husband started smoking was recorded, the duration of the wife's exposure to passive smoking could be estimated. This assumes that no non-smoking wife started smoking in the interval 1966–1981. Figure 1 of Hirayama (1984) and Kristen (1986) show a rapid rise in per capita cigarette consumption in this period in Japan. In the light of this increase, it is plausible to assume that a number of these wives became smokers after 1965. More non-smoking wives of smoking husbands

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would be expected to become smokers than among those married to non-smokers because of the husband's example. Likewise, more wives of smokers are likely to have been misclassified as non-smokers in 1965 than wives of non-smokers (Lee, in press).

In the absence of information on duration of exposure, we know only the reported smoking status of husband and wife at initial interview. Assuming stability throughout, older wives in 1965 have been exposed for longer than younger wives. If so, relative risks should increase but the opposite is true (Exhibit 7). Indeed, as has been indicated, wife's age in 1965, is a less effective explanatory variable for cumulative lung cancer mortality than husband's age. Dr. Hirayama's analyses which use the spouse's age for age standardization are of questionable value. Theories of carcinogenesis relate the incidence of cancer to the age of the experimental animal or the individual. The analytical comparisons given here indicate that husband's age *cannot* be used as a surrogate for wife's age if the age at entry of the decedent is used. The importance of this conclusion may be seen in the observation that, if Dr. Hirayama's study is excluded from a global estimate of passive smoking effects on lung cancer, the resultant meta-analysis gives a value which is not significantly greater than 1!

Dr. Hirayama's study ascertained 142,857 women 40 years or over in 1965. Figures 7 and 8 of Hirayama (1984) document the smoking history or exposure of 108,906 females, leaving 33,951 women unaccounted for. It might be assumed that 24% of the female cohort were widows in 1965 except for Dr. Hirayama's statement "information on the smoking history of the husbands of non-smoking women with lung cancer was available – in 77.3% of cases (174 out of 240)" (Hirayama 1981). This means that the 91,540 wives analysed here and in Hirayama (1984) represent 77.3% of a total of 118,422 wives in 1965. Clearly it is impossible to re-construct the total female cohort from the information given. If, as stated by Dr. Hirayama, 23% of his study group are missing, then his confidence limits are too narrow in that they do not allow for the effect of these non-sampling errors. Inclusion of non-sampling errors for the 23% missing wives totally negate his claims of significance for the association between passive smoking and lung cancer and between green and yellow vegetable intake and lung cancer.

This investigation prompts the author to call for an international panel of scientists to be given access to Dr. Hirayama's files. An independent evaluation is needed of the contribution which this unique study can make to the role of passive smoking and dietary habits in the etiology of lung cancer and heart disease.

Acknowledgement: The author is indebted to Dr. John Viren for his suggestions, criticisms and advice.

References

Breslow N (1986) Use of the power transform to discriminate between additive and multiplicative models in epidemiologic research. In: Moolgavkar SH, Prentice Ross L (eds) Modern statistical methods in chronic disease epidemiology. Wiley, New York, pp 181–196

Breslow NE (1987) Logistic regression, proportional hazards and related methods for the analysis of chronic disease risk. Presented at the German-American Seminar on Longitudinal Studies and their Analyses, Institute for Social Medicine and Epidemiology of the Federal Health Office, Berlin. June 23–26, 1986. Revised January, 1987

Breslow NE, Day NE (1980) Statistical methods in cancer research, vol 1. The analysis of case-control studies. IARC Scientific publications Number 32. Lyon, France.

Breslow NE, Day NE (1986) Statistical methods in cancer research, vol 2. The design and analysis of cohort studies. IARC Scientific publications Number 82. Lyon, France

2023381565

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Hirayama T (1981) Modern medicine (interview). Münchener Medizinische Wochenschrift 123(40):1480–1488

Hirayama T (1982) Does daily intake of green-yellow vegetables reduce the risk of cancer in man (an example of the application of epidemiological methods to the identification of individuals at low risk). In: Bartsch H, Armstrong B, Davis W (eds) Proc. of the symposium on factors in human carcinogenesis IARC sc publ no 39:531–540. Lyon, WHO

Hirayama T (1984) Lung cancer in Japan: Effects of nutrition and passive smoking. In: Mizell N, Corea P (eds) Lung cancer: causes and prevention. Chemie International, pp 175–196

Kristen MM (1986) Japanese lung cancer mortality rates 1947–1980 and per capita cigarette consumption in Japan. Int J Epidemiol 15:140–141

Lee PN (in press) Increased risk of lung cancer in non-smokers married to smokers: A result of ETS exposure or of bias? Int Archives of Occ & Enviror Hlth

Mantel N (1983) Epidemiologic investigations – care in conduct, care in analysis, and care in reporting (editorial). J Ca Research Clin Oncology 105:113–116

NRC Report (1986) Environmental tobacco smoke. Measuring exposures and assessing health effects. Committee on Passive Smoking (Barbara Hulka, Chairman). National Academy Press, Washington, DC

Payne CD (1985) The GLIM systems release 3.77. Numerical Algorithms Group, Oxford

Segi M, Tominaga S, Aoki K, Fujimoto I (1981) Cancer mortality and morbidity statistics. Japan and the world. Gann monograph on Cancer Research No 26 Japan Scientific Societies Press, Tokyo

Seidman H (1985) Age at exposure versus years of exposure. In: Garfinkel L, Ochs O, Mushinski M (eds) Selection, follow-up, and analysis in prospective studies: A workshop. NCI Monograph 67, USDHSS, NCI, Bethesda, Md, pp 205–209

Smith P, Doll R (1982) Mortality among patients with ankylosing spondylitis after a single treatment course with X rays. Br Med J 284:449–460

Tukey F, Mosteller JW (1977) Data analysis and regression. Addison-Wesley, Reading

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clearly inadequate for the purposes at hand. Rather fine categorisation is used for husband's occupation, but analysis of the data does not indicate that this is a significant predictor. The stratification for age, on the other hand, is far too coarse. Variations of cancer incidence within 10-year age ranges are large compared with the variations attributed to the husband's smoking. Even relatively small differences in the age distribution of the three populations could thus produce the reported apparent effect. The use of husbands' rather than wives' ages for stratification compounds the problem.

The measure of risk is also inappropriate for a study of such extended duration. The number of person years at risk rather than the number of subjects should be used as the exposure variable, since many subjects would have died of other causes during the study. The appropriate procedure for analysing data of this type is given in Mantel's original paper.[1]

Finally, it is clear from the original paper that Dr Hirayama analysed several causes of death, but reported statistics only for lung cancer. The procedure of reporting only the most significant result from a choice of several possible dependent measures a posteriori is a common error which naturally leads to inflated estimates of significance. Only an appropriate multivariate test can properly estimate statistical significance in this situation.

The analysis reported must thus be regarded as inconclusive unless more refined analyses are able to confirm the results. We endorse the author's suggestion that further study based on larger samples is needed, but we emphasise that such studies can be useful only if the relevant biomedical data are recorded and analysed in sufficient detail to isolate the hypothesised effect from confounding factors.

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[1] Mantel N, Halperin M. *Journal of the American Statistical Association* 1963;58:611-27.

SIR,—Most of the questions raised in my letter (3 October, p 917) were not addressed in the response of Dr Hirayama that followed. The first readings of his original paper troubled me in view of his recognised work, so that before I commented I reviewed every Hirayama paper in the literature on this study population to see if the collective information might answer the questions. A map of Japan was constructed by prefectures and minor population subdivisions and the areas of the study were marked as nearly as they could be ascertained. Review of the reports on the epidemiology and clinical aspects of lung cancer of other Japanese scientists and finally a serious study of Japanese demography, industry, disease trends, and all pertinent data were made; so the questions asked were serious and responsible.

Dr Hirayama did not answer the question about how or why the specific health stations surveyed were selected, or how the few prefectures of the total in Japan from which the health stations were chosen were selected. He admitted that the selection was not random and states, "The satisfactory representativeness of the sample was confirmed after the survey." He does not say by what criteria this was confirmed.

Mapping of the areas selected for study and of the industrial concentrations shows them to be related in nearly every instance. Dr Hirayama states, "Asbestos exposure is quite unlikely to have influenced our result since the proportion of industrial areas are surely not in excess in our sample." Asbestos and other industrial exposures would have to be considered according to the locations of the study areas and of the industrial complexes as revealed on the map of Japan. The areas were nearly all in the areas with high standardised mortality ratios in the excellent and fully documented countrywide epidemiological lung cancer mortality study of Minowa *et al*.[1] The tabulation on the basis of the husbands' ages is not explained. According to the median age at time of marriage in Japan, there is a difference between husbands' and wives' ages, the wives being generally younger. Dr Hirayama states, "We have tables by wives' ages separately." They were not found in the literature search on these data.

No response at all was made to the following questions: (1) Were the families whose medical care was covered by industry omitted from the study? (2) To what population is Hirayama referring? (3) Why were 31% of the women surveyed (and 40% of the women smokers) listed as unknown or not specified as to occupation? For a person to person survey, this suggests methodological problems. (4) Why were references to current Japanese studies by reputable men, Minowa *et al*[1] and Aoki,[2] whose findings did "not seem to explain the prefectural differences of lung cancer mortality" not mentioned? (5) The report by Ishikawa[3] on the preponderance of adenocarcinoma in Japan, in a footnote of which he acknowledges the assistance of Dr Hirayama, his colleague as a reviewer, is not referred to in the answer, although this is very important to this discussion.

Two new issues were introduced by Dr Hirayama in his response, one on the quantity of sidestream smoke inhaled by the wives, without any discussion of the quantity smoked in houses or in the presence of the wives. All the sidestream smoke of husbands' cigarettes would not be inhaled. A remarkably careful study on this subject was reported in 1978 by a French group that helps to explain the differences reported by different techniques of measurement. They improved and explained each innovation they used to overcome logistical problems noted in previous studies. They concluded, with valid proof, that on the strictly toxicological level there is no hazard for non-smokers. The report does not neglect to remark on the problems that are presented to a very important fraction of the population, however. The second issue introduced in the reply was that inhalation through the nose is different from the smoker's direct inhalation. This did not consider the superb filtering system, which would conceivably reduce the amount of ambient smoke inhaled by the wives.[4]

Finally, the far-reaching implications of this unproved passive smoking effect are already in evidence in the literature.

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[1] Minowa M, Shiraematsu I, Nagai M, Fukutomi K. *Soc Sci Med* 1981;15D(1):225-31.
[2] Aoki K, Ohno Y. *Nippon Rinsho* 1980;38:2541-50.
[3] Ishikawa S. *Jpn J Clin Oncol* 1973;3:19-30.
[4] Badre R, Guillerm R, Abran N, Bourdin M, Dumas C. *Annales Pharmaceutiques Françaises* 1978;36:443-52.

SIR,—Dr T Hirayama (17 January, p 183) reports a greater risk of lung cancer in non-smoking women when their husbands smoke than when they do not. Assessing the statistical significance of this association by a χ^2 trend statistic on one degree of freedom, Dr N Mantel (3 October, p 914) showed that a non-significant value of 3·31 is obtained if age and occupation are ignored. However, if these factors are taken into account, on the basis of data given in table I of Dr Hirayama's recent letter (3 October, p 916), a higher χ^2 value of 8·70 is obtained, which is statistically significant ($p<0·01$), and similar to, though not identical with, to the value of 10·88 given in his original paper. While this slight discrepancy might have been due, perhaps, to the use of narrower age bands in Dr Hirayama's original calculations, it is clear that the much more significant differences claimed in tables II and III of his letter are due to a statistical error.

Table II, which gives a very much higher χ^2 value of 36·81 for a similar comparison, is based on the false assumption that the lung cancer rate of non-smoking women with husbands who did not smoke is known precisely. The correct calculation, given in my table, gives a much lower level of significance for the Japanese data, and his calculations for the American[1] and Greek[2] data are similarly in error. Consideration only of women with smoking husbands has also led Dr Hirayama to conclude incorrectly that the American study was materially less powerful than the Japanese study because of sample size. In fact, the studies were of very similar power, a slightly smaller total number of deaths in the American study (153 compared with 174) being balanced by the greater stability of the denominator in the relative risk calculations, due to the greater number of deaths in women whose husbands did not smoke (65 compared with 32).

The source of the error in his table III is not clear, but the remarkably narrow 95% confidence bands for relative risk given in the table below the figure cannot be even approximately correct. How, for example, can the ratio of 2·94 given for the comparison of lung cancer rates between non-smoking men whose wives smoke (seven deaths out of 1010) and non-smoking men whose wives do not smoke (50 deaths out of 19 279) possibly have 95% limits as close together as 2·65 and 3·26—that is, ±10%—when the 95% limits for the seven observed deaths are approximately 2 and 12—that is, ±70%—and the variability of the relative risk must be greater than this?

Hugod, *et al*[3] have shown that under quite extreme passive smoke conditions, sufficient to produce a carbon monoxide air concentration of 20 parts per million, a non-smoker would take 11

Observed and expected deaths from lung cancer in non-smoking women in the Japanese study according to the smoking habit of their husbands

	Husbands do not smoke		Husbands smoke			
	Observed	Expected	Observed	Expected	χ^2	p
As given by Hirayama	32	(32·0)	142	85·8	36·81	<0·00001
Correct calculation	32	45·8*	142	128·2*	5·78	<0·05

* Standardised for age and occupation on the basis of data in table I of Dr Hirayama's letter (3 October, p 916).

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hours to take in an amount of tar equivalent to that inhaled by the smoker of an average cigarette and 50 hours to take in the equivalent amount of nicotine. Similar estimates can be made from other studies,[4-6] suggesting that *in terms of dose* one passively smoked cigarette is equivalent to a very small fraction of one actively smoked cigarette. In Dr Hirayama's study, on the other hand, elevations of lung cancer risk in active smokers of about five cigarettes a day are similar to those seen in non-smoking women married to smokers of 20 or more cigarettes a day. As these husbands are stated to smoke only 8·4 cigarettes a day at home and these presumably not all in the presence of the wife, his results are implicitly suggesting that *in terms of lung cancer response*, one actively smoked cigarette and one passively smoked cigarette are virtually equivalent.

This contrast is so striking that one must seriously doubt whether the elevated lung cancer risk seen in non-smoking wives of smokers, statistically significant as it may be, is really caused by the passive smoke exposure. It seems far more likely that the explanation lies in some hitherto undiscovered confounding or biasing factor.

PETER N LEE

Sutton, Surrey SM2 5DG

[1] Garfinkel L. *J Nat Cancer Inst* 1981;66:1061-6.
[2] Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. *Int J Cancer* 1981;27:1-4.
[3] Hugod C, Hawkins LH, Astrup P. *Int Arch Occup Environ Health* 1978;42:21-9.
[4] Repace JL, Lowrey AH. *Science* 1980;208:464-72.
[5] Hinds WC, First MW. *N Engl J Med* 1975;292:844-5.
[6] Russell MAH, Feyerabend C. *Lancet* 1975;i:179-81.

**We sent this letter to Dr Hirayama, who replies below.—ED, *BMJ*.

SIR,—Since in Garfinkel's paper the only data available were expected frequencies based on the risk for women with non-smoking husbands, similar calculations were attempted with the Japanese and Greek data and presented in table II. If Garfinkel had shown the complete data better comparison could have been made, as suggested by Mr Lee.

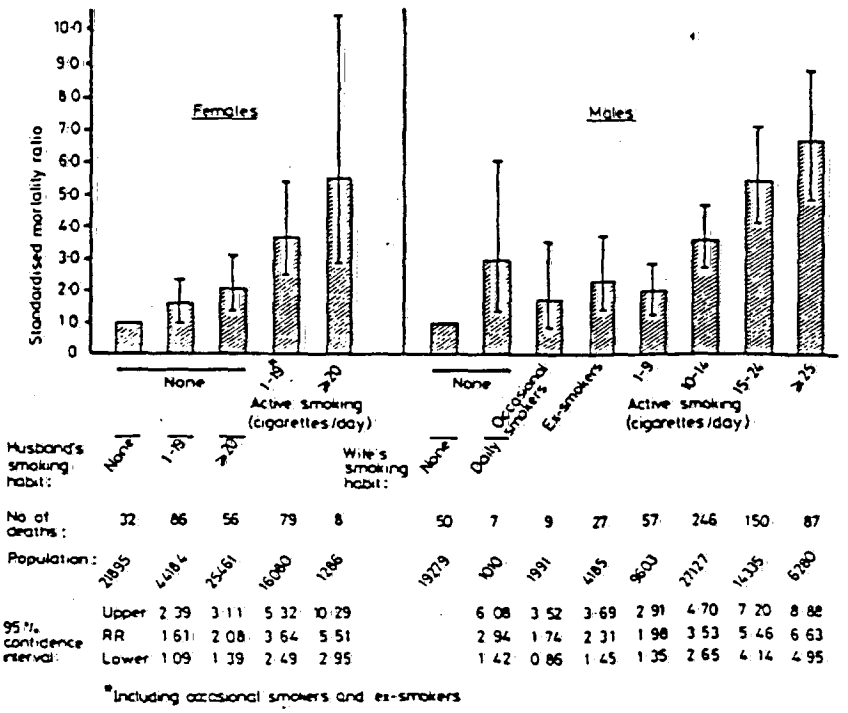
Mr Lee also worries about the data as they suggest that the risk of passive smoking is almost equivalent to that of light smoking. The only way to answer such questions must be by carrying out in-depth studies of the chronic toxicity of sidestream smoke and of health consequences resulting from prolonged exposure to passive smoking. The study by White and Froeb suggests a considerable effect on the airways from passive smoking.[1]

I regret that errors have been found in the 95% confidence intervals shown in the figure in my last letter. The correct values are given in the accompanying figure. The errors do not, however, influence the substance of my letter.

T HIRAYAMA

Epidemiology Division,
National Cancer Center
Research Institute,
Tokyo, Japan

[1] White JR, Froeb HB. *N Engl J Med* 1980;302:720-3.



	Husband's smoking habit: None	1-19	≥20	Wife's smoking habit: None	Occasional smokers*	Ex-smokers	1-9	10-14	15-24	≥25
No of deaths:	32	86	56	79	8	50	7	9	27	57	246	150	87
Population:	21895	44184	25461	16080	1286	19279	1090	1991	4185	9603	27127	14335	6780
95% confidence interval: Upper	2·39	3·11	5·32	10·29		6·08	3·52	3·69	2·91	4·70	7·20	8·88	
RR	1·61	2·08	3·64	5·51		2·94	1·74	2·31	1·98	3·53	5·46	6·63	
Lower	1·09	1·39	2·49	2·95		1·42	0·86	1·45	1·35	2·65	4·14	4·95	

*Including occasional smokers and ex-smokers

Active and passive smoking and standardised mortality rates for lung cancer: relative risks (RR) with 95% confidence intervals—prospective study, 1966-79, Japan. (Revised version of figure published 3 October, p 917.)

Diseases of modern civilisation

SIR,—Certainly we can all agree with the Revd H C Trowell and Dr D P Burkitt (7 November, p 1266) that there are several conditions that are uncommon in developing countries but have become increasingly common in the West. They add that in their book *Western Diseases: Their Emergence and Prevention* "there is little hard evidence that would warrant a recommendation for dietary change in these countries."

There is, however, a great deal of evidence, from experiments with laboratory animals and with human subjects, that one item in Western diets, in the quantities now commonly being consumed, produces a range of abnormalities that indicate its likely involvement in producing some of the Western diseases (references given in a recent paper[1]). Here is an abbreviated list: increased concentration of cholesterol and triglyceride, decreased concentration of high-density lipoprotein cholesterol, increased concentration of insulin and corticosteroids, and increased concentration of uric acid in the blood; impaired glucose tolerance; diminished tissue sensitivity to insulin; increased adhesiveness and aggregation of blood platelets; paradoxical electrophoretic behaviour of blood platelets; retinopathy; nephropathy indistinguishable both histologically and biochemically from that seen in diabetes mellitus. It is difficult to imagine that more evidence is needed to indict sugar as a likely cause of at least two of the "Western diseases," coronary heart disease and diabetes.

The average consumption of sugar is now about 1 kg a week in Western countries, 25 times what it was before the industrial revolution. Some people take two or three times this average. I see no problem about what should be the most sensible dietary recommendation we could be making.

JOHN YUDKIN

London NW3

[1] Yudkin J. *Am J Clin Nutr* 1981;34:1453.

Alcohol and alcoholism

SIR,—Dr Richard Smith's series of papers on alcoholism (26 September, p 835; 3 October, p 895; 10 October, p 972; 17 October, p 1043; 24 October, p 1108; 31 October, p 1170, and 7 November, p 1251) was timely and generally accurate and comprehensive, but I was surprised to see no reference to supervised disulfiram—one treatment which does seem to be of specific benefit in alcoholism. This has been shown in three well-designed controlled trials and there are no contrary findings. All the studies stress that supervised disulfiram is an extension of the therapeutic relationship and not a substitute for it.

Gerrein *et al*[1] found that 85% of patients given disulfiram twice weekly under supervision remained in treatment, compared with a maximum of 39% in patients who had once-weekly supervised disulfiram or unsupervised disulfiram treatment. The figures for those abstaining for a minimum of eight weeks were 40% compared with a maximum of 15%. Azrin[2] reported that for patients given the same intensive community-based psychotherapeutic and rehabilitative programme, those in whom the administration of disulfiram was supervised—usually by their wife—did vastly better than those on unsupervised medication. Drinking days were 2% for the supervised group against 55% for the unsupervised. Unemployment was 20% against 56%; and time spent in institutions was nil against 45%. This last figure has obvious financial implications. In an employee treatment programme, Robichaud *et al*[3] found that absenteeism averaged 9·8% before treatment, 1·7% during treatment with twice-weekly supervised disulfiram given by the factory nurse, and 6·7% when treatment was discontinued. All these studies used a standard dose of disulfiram, which was probably inadequate for some patients, and no alcohol challenge was done.

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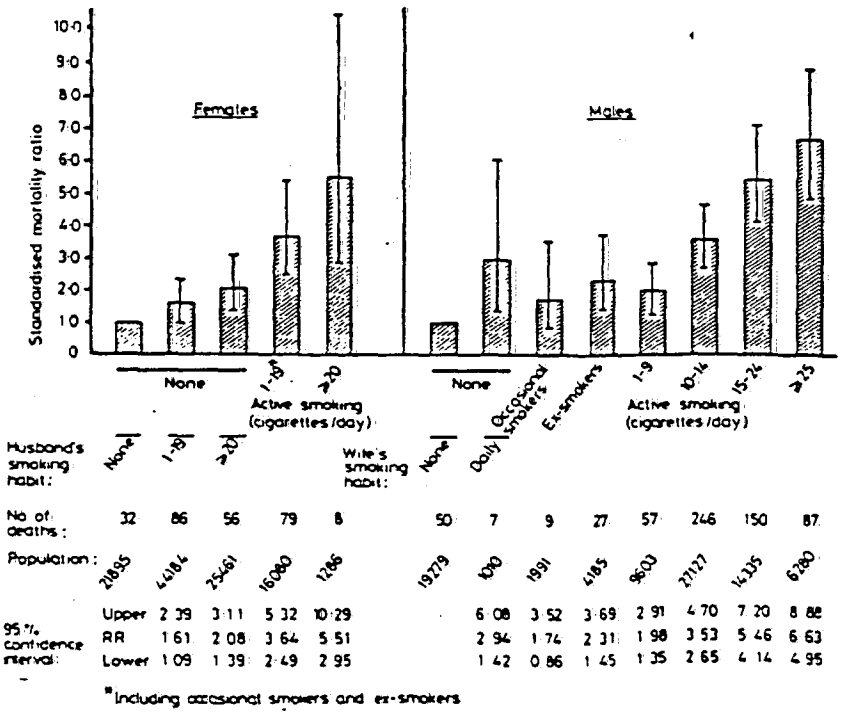

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PRESENT AND FUTURE OF INDOOR AIR QUALITY

Proceedings of the Brussels Conference,
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Editors:

C.J. Bieva, Y. Courtois and M. Govaerts

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ASSESSING THE VALIDITY OF A JAPANESE COHORT STUDY

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INTRODUCTION

Results of a Japanese cohort study published by Takeshi Hirayama (3-6) have been influential in the assessment of cancer risks of non-smoking women exposed to environmental tobacco smoke (ETS) through their husbands' smoking. We compared mortality projections, based on Japanese national death rates, with the reported cohort mortality. These comparisons revealed serious external and internal inconsistencies in the study results:

* Reported cohort death rates were lower than those for all Japan, apparently because mortality tracing was incomplete and death rates among those lost to follow-up were higher than among those traced.

* Cohort mortality deficits varied greatly among sub-cohorts defined by entry age and marital status.

These inconsistencies raise the possibility that selection biases are present in the data which might distort comparisons between exposed and non-exposed groups.

COHORT SELECTION AND FOLLOW-UP

* The cohort was recruited in the last quarter of 1965 from 49 geographic areas within 29 Health Center Districts in 6 Japanese prefectures.

* Of persons aged 40-79 in the survey areas, 95% were included in the cohort (prefecture range: 91% to 99%). "Only those persons found healthy" were recruited. The criteria for exclusion on health grounds were not reported.

* The age distribution of the cohort was similar to that of the 1965 Japanese population, except that the cohort under-represented the 70-79 age group.

* The cohort was followed for 16 years to the end of 1981. The number of subjects lost to follow-up was not reported.

LIFE TABLE PROJECTIONS

Hirayama reported that age-specific mortality rates in the cohort, for all causes of death and for specific causes, were similar to those in the Japanese population. In fact, crude death rates for the 16-year study period, calculated by dividing reported total deaths by person-years of observation, were substantially lower than what would be expected from national death rates (Table I).

We arrived at this conclusion by constructing mortality projections for the

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cohort, based on standard demographic life table procedures. Japanese death rate statistics were obtained from U.N. Demographic Yearbooks (7) for all-cause mortality, and from the Gann Monograph (2) for cancer mortality. The life tables provide year-by-year projections of cumulative deaths and person-years by age at observation. Cause-specific mortality projections were obtained by applying cancer death rates to the person-year projections. For smoking-specific sub-cohorts, adjustments to the published death rates were made by using the reported cohort mortality ratios for smokers versus non-smokers.

MORTALITY IN PERSONS LOST TO FOLLOW-UP

Total reported deaths in the cohort were 16,000 fewer than total projected deaths. For males, reported deaths were 8,600 (22.5%) less than projected, and for females reported deaths were 7,400 (25.5%) less than projected.

From the reported numbers of deaths, we calculated the numbers of person years which would have been observed in the cohort if there had been 100% follow-up. At the end of the 16-year study period, the totals of these calculated person-years were 108,000 more than reported person-years for males, and 95,000 more than reported for females. Those differences show that follow-up of the cohort must have been less than 100%. This conclusion is derived entirely from the reported cohort deaths and person-years of observation, and is not in any way based on the life table projections. Assuming that on the average 8 years of observation were lost per untraced person, an estimated 25,000 subjects, or about 10% of the whole cohort, were lost to follow-up.

The life table projections suggest that some 16,000 cohort deaths were not traced. That number is 64% of the estimated 25,000 persons lost to follow-up, as compared with approximately 21% of reported deaths among the cohort members who,

TABLE I

CRUDE DEATH RATES PER 100,000 PERSON-YEARS

	Males			Females		
	Projected Rate	Reported Rate	% of Projected	Projected Rate	Reported Rate	% of Projected
All Cause	2,300	1,824	79*	1,409	1,069	76
All-site Cancer	575.3	500.4	87	329.9	263.4	80
Lung Cancer	86.6	81.3	94	24.9	21.1	85

* Reported crude death rate as a percentage of projected.

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according to our estimates, were not lost to follow-up. This mortality differential is a possible explanation for the differences between reported and projected death rates noted above. In fact it is the most likely reason, since the alternative explanations discussed below seem inadequate to account for differences of the magnitude observed.

OTHER EXPLANATIONS FOR MORTALITY DEFICITS

We considered whether the discrepancy between reported cohort death rates and national rates could be explained by sampling variation, by lower death rates in the geographic areas represented in the cohort, or by "healthy person" effects.

* The size of the cohort is too large for sampling variation to be a credible explanation. For example, a 95% confidence interval for the ratio of reported to projected all-site cancer mortality among women is 78% to 82%.

* Japanese vital statistics by prefecture show regional variations in cause- and age-specific death rates, but these prefectural statistics do not suggest that death rates in the cohort as a whole would have been substantially lower than national rates. Thus it seems unlikely that regional variations could explain rate differentials of the magnitude indicated by the life table projections.

* Since there were some exclusions from the cohort on health grounds, one would expect an initial healthy person effect. However, examination of the ratios of reported deaths to life table projections in intervals of the 16-year study period shows that there were still very substantial cohort deficits in the last years of the study, and it is unlikely that a healthy person effect would persist strongly for so long in a cohort with entry ages of 40 to 79 years.

THE NON-SMOKING MARRIED WOMEN COHORT

At the beginning of the study period, the cohort contained 91,540 non-smoking married women (NSMW). A total of 16,181 deaths were projected for the NSMW, and 9,106 were reported. For all-causes, all-site cancer, and lung cancer, the percentages of reported to projected mortality for the NSMW were 56%, 67%, and 72% respectively. The remarkable feature of these projections is that while the mortality deficits relative to projections are very large for the NSMW (44%, 33%, and 28% for all-causes, all-site cancer, and lung cancer respectively), they are quite small for all other women (3%, 6%, and 3% respectively).

To investigate whether this pattern could be due to marital mortality differentials, we constructed a life table based on 1975 Japanese marital status-specific death rates (2). The result of our analysis was that reported total deaths were 63% of projected for the NSMW sub-cohort, while the ratio for all other women was 96%. Thus it appears that marital mortality differentials can explain only a

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small part of the differences between the NSMW and other women in the reported versus projected mortality deficits.

When we compared reported and projected lung cancer mortality for the NSMW by entry-age decade, another internal inconsistency became apparent. Reported lung cancer mortality was only 51% of projected for the 60-69 entry-age group, while for younger women (40-59 years at entry) reported mortality was 84% of projected.

CONCLUSIONS

In their monograph on the design and analysis of cohort studies, Breslow and Day (1) note that: "The validity of a cohort study depends fundamentally on complete ascertainment of the events of interest (e.g., cancer death) ... ." Our analyses strongly suggest that reported death rates in the Hirayama cohort were substantially lower than Japanese national rates because mortality among persons lost to follow-up was higher than among those successfully traced. If this explanation is correct, it is possible that biases exist in the data which might invalidate an observed relationship between exposure to ETS and mortality. Such biases could arise, for example, if there were more complete ascertainment of vital status among those exposed than among those not exposed. The striking internal inconsistencies described above, between sub-cohorts defined by marital status and entry age, reinforce these doubts about the validity of the study.

REFERENCES

1. Breslow NE, Day NE (1987) The Design and Analysis of Cohort Studies. IARC, Lyon

2. Gann Monograph on Cancer Research No. 26 (1984) Segi, M et al (eds). Japan Scientific Societies Press, Tokyo

3. Hirayama, T (1967) Internal Report. National Cancer Center Research Institute, Tokyo

4. Hirayama, T (1970) Interim Report of Medical Research on Human Cancer. National Cancer Center Research Institute, Tokyo

5. Hirayama, T (1981) British Med J 282:183-185

6. Hirayama, T (1984) Preventive Med 13:680-690

7. United Nations (1972, 1985) 1971 and 1983 Demographic Yearbooks. United Nations Press, New York

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A dose-effect relationship in the development of malignancy is undisputed. Passive smokers living and working in smoke-infested rooms will take up smoke mainly through the nose (like pipe smokers), using the natural filter that smokers evade. (This explains the fact that the lung cancer rate is not raised among non-inhaling pipe smokers and cigar smokers.) The side-stream smoke, involuntarily taken up by the passive smoker, does still contain a high level of the noxious substances contained in tobacco, but they are diluted and weakened by normal room ventilation.[11] If we assume that the effect of 20 "passively smoked" cigarettes approximately equals that of one "active" (inhaled) cigarette, the carcinogenic substances diluted in this smoke would have to act at incredibly low concentrations to produce the alleged effect. In view of the dose-effect correlation this is highly improbable.

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3 Weber A, Jermini C, Grandjean E. *Am J Publ Health* 1976;66:672-6.
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5 Schilling RSF, Letai AD, Hui SL, Beck GJ, Schoenberg JB, Boubuys A. *Am J Epidemiol* 1977;106:274-83.
6 Surgeon General. *Smoking and health—a report of the Surgeon General.* Washington DC: US Department of Health, Education, and Welfare, 1979.
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3 Leung JSM. *Br J Dis Chest* 1977;71:273.
4 Sato T. *Bull Inst Publ Health (Tokyo)* 1961;10:31-5.
5 Sterling T, Weinkam J. *J Occ Med* 1976;18:743-55.
6 Sterling T, Weinkam J. *Arch Environ Health* 1978;33:313-7.
7 US Department of Health, Education, and Welfare. *Use habits among adults of cigarettes, coffee, aspirin, and sleeping pills.* Washington DC: Government Printing Office, 1979.
8 Todd GF. *Social class variations in cigarette smoking and in mortality from associated diseases.* Occasional paper 2. London: Tobacco Research Council, 1976.
9 Statistics Bureau. *Japan statistical yearbook.* Tokyo: Prime Minister's Office, 1980.

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7 US Department of Health, Education, and Welfare. *Use habits among adults of cigarettes, coffee, aspirin, and sleeping pills*. Washington DC: Government Printing Office, 1979.
8 Todd GF. *Social class variations in cigarette smoking and in mortality from associated diseases*. Occasional paper 2. London: Tobacco Research Council, 1976.
9 Statistics Bureau. *Japan statistical yearbook*. Tokyo: Prime Minister's Office, 1980.

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Life-Style and Mortality

A Large-Scale Census-Based Cohort Study in Japan

T. Hirayama
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41 figures and 37 tables, 1990

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Contributions to Epidemiology and Biostatistics

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The author and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Der Kassenarzt
Deutsches Ärztemagazin · Nr. 51/52 · Dezember 1987

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Franz Adlkofer

Probleme mit dem Passivrauchen

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Der Kassenarzt, (1987), 27:(51/52), pp. 29-39

(uncertified translation)

Franz Adlkofer

The Problems of Passive Smoking

People are faced day and night with reports about the presence of noxious, in particular carcinogenic, substances in almost all spheres of life. They are found in our food and drink etc. just as much as in the air we breathe. Thereby the impression is created that all these substances are man-made and the result of industrialisation. In truth many of them occur throughout nature and mankind has been exposed to them since the beginning of phytogenesis. In order to survive at all in such a hostile environment, Man has over millions of years developed effective defence systems, already recognised by Paracelsus and reflected in his doctrine: "dosis facit venenum". Whether this applies to carcinogenic substances too, which would be plausible, is at present the subject of controversial discussion. There are those who are convinced that the biological defence systems only break down if they are metabolically over-loaded; there are ample examples of this. They do not believe that the simple mechanistic view is tenable according to which injury to health occurs in direct proportion to the cancerogenic substances absorbed and thus believe in the existence of a threshold in respect of these substances. In contrast, there are others who will not budge from their opinion that even one cigarette per day or one puff from a cigarette or even the fact of passive smoking will contribute to bring about cancer some decades later. This controversy will endure until we understand the molecular and cellular mechanisms which trigger off cancer in individuals -- and we are still far from that day. The following article is intended to show the present state of scientific research into the problem of passive smoking, which leads us to the conclusion that a minimal risk to health through passive smoking cannot be either excluded or proved.

The historical background

In Europe the battle of Authority against smoking goes back to the 17th century. The many prohibitions against smoking issued in almost all countries were based on a variety of reasons, but hardly ever on the grounds of it being a nuisance, let alone a possible risk to the health of non-smokers. It was left to our Federal Government to recognise, at the beginning of the seventies, "with adequate certainty that the proved injury to health through smoking can also occur through passive smoking in the same way although to a lesser degree" (Bundestag Printed Matter 7/2070). This is the more astonishing as, at that time, scientific research into passive smoking had not even begun in earnest. To what extent such an evident analogism can be used

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to justify a statement of that nature was not even investigated at the time. At any rate the world of science felt called upon to pay more attention to the problem of passive smoking. In so doing it was following a world-wide trend which had been set in motion and which was being maintained by the ever more heated discussion about the risks to health through smoking. To date a vast number of papers have been published and many congresses held on the subject of passive smoking. Two original papers and two review articles stand out from the almost overwhelming mass of literature. The two original papers, of which one is scientifically without value and the other subject to a great deal of doubt, have contributed to heating up the discussion about passive smoking throughout the world, whereas the review articles, which differ greatly in quality, have done the same within the Federal Republic.

In 1980, the 'New England Journal of Medecine' published the results of a study by White and Froeb showing that chronic exposure to tobacco smoke at work brought about a significant deterioration in the lung function of non-smokers. So far as the authors were concerned, and those who wanted to believe it, this paper for the first time provided proof of the harmfulness of passive smoking. In fact, however, the results obtained by White and Froeb are not scientically tenable. Professor Lebowitz, one of the co-authors of the American Surgeon General's Report, for instance, declared the following at a hearing in Washington: "The basic problem with the White and Froeb study is that it was ill-planned from the epidemiological point of view. The difficulties are inherent in the paper from its very beginning to the statistical analysis and affect all data and the conclusions. The fact that some time between 1976/77 and the time when the study was published 3000 people were taken out of it, whereby the results suddenly became significant, is particularly remarkable. Unfortunately Dr. White cannot remember why he removed these 3000 people from his study." Following a visit to Dr. White, Professor Gostomzyk, Head of the Health Office of the city of Augsburg and Dr. Heller of the Institute for Mathematical Economic Theory of Karlsruhe University commented in a similar manner. They summarised their impressions as follows: "The working methods of Dr. White are not those of a scientist but are more like those of a layman convinced of his ideas". Quite irrespective of this shattering assessment the work fulfilled its purpose in that for the first time it rendered smokers responsible for damaging the health of their fellow-men. It enabled Dr. White who is a sports teacher and active in the Californian anti-smoking movement to influence a plebiscite in California on smoking in public places and at work. In addition it is quoted by other authors whenever the injurious effect of passive smoking on the lung function of non-smokers is emphasised. In "Berichte (Reports) 3/86" of the Federal Office for the Environment it is even regarded as the only paper of its kind which can withstand criticism. It is therefore not to be wondered at that the Council of Experts on the Environment

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used it to bolster up the ideas contained in its recently completed Expert Opinion.

One year later there appeared in the 'British Medical Journal' the publication of Hirayama's further results of a cohort-study begun in 1965 on the influence of life-style and environmental factors on the origins of disease in Japan. A side-result of this study had been that non-smoking wives of smoking husbands die more frequently of lung cancer and - for whatever reason - commit suicide more often than non-smoking wives of non-smoking husbands. This study, which even today remains the most important of all the epidemiological studies undertaken into the problems of passive smoking and which has provided a new dimension for the discussion of this issue, constitutes a watershed. For some it is the final proof of the risk of cancer through passive smoking, for others it is no more than an unscientific fabrication in which figures were manipulated until they attained the desired level of significance for the dose/response ratio. Whatever may be right, the study leaves many questions open and there are hypotheses on the basis of which the findings can be explained without reference to passive smoking. The real scandal however is that Dr. Hirayama is neither willing nor can be forced to lay his original data open for examination. Only a few weeks ago he answered with a smile an invitation to do so at a Tokyo symposium.

In 1985 the Senate Commission of Enquiry into Substances Noxious to Health included passive smoking in the MAK-List. In a detailed statement of motive, it endeavoured to justify its suspicion of passive smoking as being carcinogenic. In so doing the Senate Commission was aware of the fact that the causal link betwen passive smoking and lung cancer is the subject of controversial discussion and that the available epidemiological findings can at best indicate a serious hypothesis. According to its principles, carcinogenic substances should if possible be wholly shunned at work or, where this is not possible, they should be kept as low as possible, since the Commission does not assume there to be threshold values for these substances. Because tobacco smoke contains mutagenic and carcinogenic substances the Commission considers the inclusion of passive smoking in the MAK-List to be obligatory and it even feels that this would have been possible many years ago. It does, however, seem doubtful whether any relevant statement concerning dangers to health through passive smoking can be made on this basis without it being backed by any epidemiological findings or animal experiments. From the point of view of preventive medecine it would be necessary to quantify the risks in order to establish priorities for protective measures. But it is just this that the Senate Commission declares to be impossible at present.

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This year the Tübingen toxicologist Professor Remmer, who is a member of the Senate Commission and a zealous supporter of the inclusion of passive smoking in the MAK-List, published a paper in the 'Deutsche Medizinische Wochenschrift' in which tobacco smoke is described as the most dangerous noxious substance to man in the air we breathe. He had noticed that in many epidemiological studies the difference in the risk of lung cancer through smoking and through passive smoking was too small for the risk incurred through passive smoking to be plausible. To explain this evident discrepancy Professor Remmer based himself on some very arbitrarily selected literature in order to draw up a theory according to which active smoking may cause far less cancer than passive smoking. It is believed that certain compounds contained in the mainstream smoke induce enzymes which detoxify the carcinogenic substances. Whereas in the sidestream smoke, to which passive smokers are exposed, these compounds are only found in ineffectively weak concentrations. Therefore, in contrast to what happens in the case of active smoking, very small quantities of inhaled carcinogenics could become fully effective. This theory is not supported by any scientific findings. Interpretation has taken the place of findings, which stands the process of acquiring knowledge on its head, as has been noted by the Research Council on Smoking and Health in a letter to the editor of the 'Deutsche Medizinische Wochenschrift'.

The Driving Forces

Bearing in mind the many risks to health to which we are daily exposed, passive smoking, which is considered a non-problem by many scientists, takes up an astonishing amount of room in public discussion. The question arises as to what may be the reasons which, despite the factual situation, keep the discussion on passive smoking going, and render it ever more passionate. I should like to pinpoint some of these reasons as follows:

Environmental consciousness has considerably increased in the course of the past decade. Therefore successful efforts have been made to reduce air pollution in our large cities and industrial conurbations as well as at the place of work without, however, even nearly attaining the desired goal of nil-pollution. More attention is being paid to indoor air pollution to which tobacco smoke contributes to a considerable degree because of the wide-spread habit of smoking. Modern methods of chemical analysis make it possible to discover even the minutest quantities of noxious substances. Although this is far from telling us anything about their toxicological significance, a need to act is created because people believe that ever less pollution must lead to ever better health. They leave out of account the doctrine of Paracelsus, which says that "the dose makes the poison."

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Responsible politicians interested in health issues are bound to act in the interests of the people entrusted to their care, as soon as they are "adequately certain" that passive smoking may lead to a health risk for non-smokers. They cannot afford to wait until "a line of sick people, invalids and dead bodies can be produced to prove that they have fallen victim to passive smoking" as it was expressed in a Bundestag Printed Matter of 1974. Since politicians can hardly themselves have the scientific training to assess the risks, they must rely on the knowledge of others. This offers lobbies a chance to influence health policy decisions in one way or another.

A pluralistic society such as ours has lobbies. And it is they who have by now removed the subject of passive smoking from scientific discussion and have put it on the political stage. It would be wrong to impute this to bad intentions. Inadequate or biassed occupation with the problem, or general insecurity with regard to scientific comprehension, are quite enough.

- There are certain branches of industry and their corresponding trade associations who seem to believe that the term occupational cancer has lost its raison d'être. So far as they are concerned lung cancer stems from smoking only, and in the case of a non-smoker, well then it is due to passive smoking. The trade unions would be well advised to discover the error of their ways in good time and to protect their members from its pernicious consequences.

- There are anti-smoking movements which, after years of guerilla warfare against smoking, have had to realise that smokers react with surprising indifference to reproaches of self-inflicted injury or being a nuisance to others. It is the aim of the anti-smoking movements to bring about a smoke-free society by the year 2000. The means to attain this end is the social ostracism of smoking. No argument is better for this purpose than to maintain that by their inconsiderate behaviour smokers endanger the health of their fellow-men.

- Certainly the cigarette industry would also have liked to intervene in the process of shaping public opinion. After all, 90% of the public by now believe that the harmfulness of passive smoking has been proved and is hardly less than that of active smoking. But the industry's chances are poor, since it has an economic interest in the matter, and has a reputation for greed into the bargain.

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Tobacco Smoke in Enclosed Spaces

Tobacco smoke in enclosed spaces consists of a mixture of about 15/20% exhaled mainstream smoke and 80/85% sidestream smoke. The mainstream component is very different from the sidestream component. Both originate in the burning zone of the cigarette, but at different temperatures. Mainstream smoke is inhaled by the smoker and in part exhaled again. Sidestream smoke originates between the puffs taken by the smoker and is released directly into the room, where it is diluted. Mainstream and sidestream tobacco smoke in a room are composed of a gaseous and a particle phase. More than 90% of the weight is accounted for by the gaseous phase. Quantitatively significant compounds are: vapour, carbon dioxide, carbon monoxide, ammonia, aldehyde and nicotine. Tobacco smoke in the room contains mainly the same substances as the mainstream smoke. Table 1 shows the concentrations of main and sidestream smoke in the air of the enclosed space under approximately realistic conditions.

There does not at present exist any reliable marker for tobacco pollution in enclosed spaces. The reason for this is that the sidestream smoke from cigarettes, cigars and pipes differs from product to product, that smokers as individuals and as between individuals produce different amounts of main and sidestream smoke, and that tobacco smoke in the air rapidly changes its composition as it ages. In addition, air in an enclosed space often contains substances which do not stem from tobacco smoke, and in some cases this kind of pollution can be greater than that caused by the tobacco smoke. Nicotine seems to be the most suitable marker for tobacco smoke in an enclosed space; 95% of it is part of the gaseous phase and not of the particle phase as in the mainstream smoke. Nicotine occurs in the enclosed air only if in fact there has been smoking. Carbon monoxide and other substances are less suitable as markers. They can only be employed where the basic pollution has been established first.

Undiluted sidestream smoke contains larger quantities of some carcinogenic substances such as polycyclic aromatic carbohydrates and volatile N-nitroso-compounds than are contained in the mainsmoke stream. Accordingly, the carcinogenic potential of sidestream smoke could be a little greater than that of the mainstream smoke, given equal quantities of substance. In their 1967 test on the skin of mice Wynder and Hoffman found that an application of condensate from sidestream smoke caused more tumors than an application of condensate from mainstream smoke. The gaseous phase was wholly neglected in this experiment. The same working party carried out inhalation experiments with hamsters, but no histological results are yet available. Astonishingly enough, however, the animals treated with main- and sidestream smoke lived longer than the untreated control animals.

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One problem in comparing the carcinogenic potential of main- and sidestream smoke lies in the fact that mainstream smoke is immediately inhaled whilst sidestream smoke ages when released into the air and thereby loses much of its toxic potential. It is not known to what extent this is also true for its mutagenic and carcinogenic potential. The one thing that is sure is that in the course of time its composition changes considerably because of dilution, evaporation, oxidation, other chemical reactions, and selective surface absorption. The few available comparative studies of main- and sidestream smoke, which were mainly carried out to measure mutagenic potential are either faulty or have produced contradictory results. Nevertheless, some scientists still insist that tobacco smoke in an enclosed space is more carcinogenic than mainstream smoke. This hypothesis is based on a comparison of fewer than 100 substances -- of the 3800 compounds identified in tobacco smoke, this is a very modest fraction. It leaves out of account both the very considerable dilution of sidestream smoke in the enclosed air and the ageing process.

As compared with former times, sidestream smoke to-day releases fewer mutagenic and carcinogenic substances since the smokers of modern cigarettes produce more mainstream and less sidestream smoke because of the halving of the nicotine and condensate content which has taken place over the years. The reason for this lies in the lower tobacco content in cigarettes and improved filter techniques. It is likely that the reductions reach up to 20%. The figures obtained with smoking-machines, which argue in favour of a disproportionately high release of carcinogenic compounds in the sidestream smoke do not reflect this development because smoking-machines simulate the smoking habits of the nineteen-fifties.

Studies undertaken so far show that the components of tobacco smoke are variously distributed in the main- and sidestream as well as in the indoor air. For that reason alone it is not possible to extrapolate from the risks of the smoker to those of the passive smoker.

Inhalation of Tobacco Smoke through Passive Smoking

Effects of passive smoking on health can be expected if the noxious substances thus inhaled are sufficient to overcome the physiological defence system of man. Only a little more than 10% of the particle phase of tobacco smoke is retained in the respiratory passages according to Hiller. Only part of this is resorbed, since the lungs have an effective cleansing mechanism. In contrast to this, something between 45% and 95% of the particle phase of the mainstream smoke is retained in the lungs of the smoker, this smoke being highly concentrated as compared with the tobacco smoke in the enclosed space. Of

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the gaseous phase of tobacco smoke in the enclosed air, mainly those compounds are resorbed in the nose and throat area and the upper respiratory tracts, which are easily soluble in water and/or chemically highly reactive. They are substances such as: formaldehyde, acetaldehyde acrolein, acetone, ammonia, and possibly also nicotine, ozone and free radicals. Insoluble and not highly reactive compounds such as carbohydrate can indeed reach the alveolar space of the lungs, but their rate of retention is very low. The mainstream smoke contains the major part of carcinogenic compounds in the particle phase. Whether this is also true of tobacco smoke in an enclosed space is not known, though there are some indications that this may be so.

Table 1

Important substances of tobacco smoke in mainstream smoke (HSR) and sidestream smoke (NSR) of cigarettes in an enclosed air space under approximately realistic conditions.

Substance	HSR Quantity/ Cigarette	NSR	Concentration in enclosed space
Carbon monoxide (CO)	2-20 mg	46-61 mg	3,6-24 mg/m3 (3-20) ppm.
Nitrogen oxide (NO)	0,07-0,17 mg	1,6-3 mg	83-333 ug/m^3 (50-200 ppb)
Nitrogen dioxide (NO_2)	n.n.	0,16 mg	19-132 ug/m^3 (10-70 ppb)
Ammonia (NH_3)	50 ug	5300-8500 ug	100-450 ug/m^3
Cyanide (HC)	150-550 ug	100-250 ug	10-120 ug/m^3
Formaldehyde	20-90 ug	450-1500 ug	20-100 ug/m^3
Acetaldehyde	18-1400 ug	2400 ug	400-500 ug/m^3
Acrolein	25-140 ug	925 ug	15-25 ug/m^3
Nicotine	0,5-2 mg	3-4 mg.	20-100 ug/m^3
Phenol	10-130 ug	270-320 ug	< 1-20 ug/m^3
Benzol	10-100 ug	488 ug	5-16 ug/m^3
Volatile Nitrosamines			
NDMA	0,2-20 ng	155-398 ng	5-70 ng/m^3
NDYR	2,4-29 ng	7-150 ng	1-5 ng/m^3
Nitrosamines specific to tobacco			
NNN	0,20-5,5 ug	0,15-6 ug	< 1-6 ng/m^3 3)
NNK	0,1-4,2 ug	0,2-0,8 ug	< 2-11 ng/m^3 3)
Benzo(a)pyrene	10-50 ng	25-103 ng	3-25 ng/m^3
Cadmium	100 ng	430-720 ng	9-31 ng/m^3
Particles (TPM)	5-30 mg	20-50 mg	0,1-0,5 mg/m^3

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Attempts have been made to quantify, with the aid of various biochemical markers, the absorption of tobacco smoke through smoking and passive smoking. A reliable marker should be tobacco-smoke-specific and should, in resorption, behave as those substances which entail the greatest risk to health. Compounds which are resorbed in the nose and throat area should therefore, not be used to assess the risks of lung cancer. Biochemical markers which would answer these requirements are not yet known. The most suitable seems to be cotinine, a nicotine metabolite. Nicotine and cotinine in body fluids prove exposure to tobacco. However, it is difficult, or even impossible, to quantify the exposure. In passive smoking nicotine acts only partly like the mutagenic and carcinogenic compounds of the particle phase. Tobacco smoke in enclosed air contains it in the gaseous phase, as has been pointed out, and not in the particle phase as is the case with mainstream smoke. Nicotine occurs as a base and is more quickly resorbed in this form than the protonised nicotine of the mainstream smoke. To some extent this already happens in the nose and throat area and the upper respiratory tracts. Nicotine, the half-life of which is short at 30 minutes is also differently metabolised as between one individual and another. In passive smokers the half-life of cotinine, which is 15 to 25 hours in smokers, is further reduced. The cotinine level in the serum, and the nicotine and cotinine excretion in urine are considerably influenced thereby, so that they are only of limited value as a measure for the absorption of tobacco smoke. In no circumstances should such data be considered suitable for the assessment of the lung-cancer risk. This is true even where they may show a correlation with tobacco pollution, as has emerged from some experiments. Nonetheless some authors maintain the view that passive smokers inhale up to 1% of the amount of tobacco smoke inhaled by smokers and conclude therefrom that they are exposed to about 1% of the risk to which smokers are exposed. Table 2 shows the nicotine and cotinine concentrations in the body fluids of smokers and passive smokers.

Alongside nicotine, carboxyhaemoglobin and thiocyanate contained in serum are also used to measure the exposure of non-smokers to tobacco. They are however even less suited than nicotine or cotinine to establish the exposure to tobacco. Carbon monoxide which is formed in the body's own metabolism normally leads to an approximately 0.7% concentration of carboxyhaemoglobin. As a rule no increase, or only a small increase, is found in passive smokers. It is only under extreme conditions and after an exposure to tobacco of several hours that a carboxyhaemoglobin value of 2% can be attained. Thiocyanate stems from hydrogen cyanide which also occurs in tobacco smoke. Both carbon monoxide and hydrogen cyanide (or cyanide ions) are tobacco-smoke unspecific and can be found in the air or in food, and also in concentrations which can be much higher than those found in tobacco smoke in enclosed spaces.

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Groups studied/Exposure	N	Result	Literature
Clinical Staff			
- not exposed (a.m.)	30	Nicotine in urine: 7.5 ± 8.3 ng/ml	Feyerabend et al 1982
- exposed (a.m.)	26	Nicotine in urine: 21.6 ± 28.8 ng/ml	
- cigarette smokers (average inhalers)	32	Nicotine in urine: 1343.4 ± 1699.8 ng/ml	
Patients and Clinical Staff			
- not exposed	22	Cotinine in urine: 2.0 ng/ml (Median)	
- exposed	199	Cotinine in urine: 6.0 ng/ml (Median)	
- Cigarette smokers	131	Cotinine in urine 1645.0 ng/ml (Median)	Wald et al. 1984
Husbands			
- non-smoking wife	101	Cotinine in urine: 8.5 ± 1.3 ng/ml	Wald and Ritchie 1984
- smoking wife	20	Cotinine in urine: 25.2 ± 14.8 ng/ml	
Clerical Staff			
Blood samples at 11.30 and 19.45 (in between, two hours in a smoke-filled bar)	7	11.30 / 19.45 Nicotine in Plasma 0.8 / 2.5 ng/ml Nicotine in urine 10.5 / 92.6 ng/ml Cotinine in Plasma 1.1 / 7.3 ng/ml Cotinine in Saliva 1.5 / 8.0 ng/ml Cotinine in urine 4.8 / 12.9 ng/ml	Jarvis et al. 1983
Ambulant patients			
- non-smokers, not exposed	46	Nicotine in plasma: 1.04 ng/ml Nicotine in urine : 3.87 ng/ml Cotinine in plasma: 0.82 ng/ml Cotinine in saliva: 0.73 ng/ml Cotinine in urine: 1.55 ng/ml	Jarvis et al. 1984
- non-smokers, exposed	54	Nicotine in plasma: 0.77 ng/ml Nicotine in urine: 12.11 ng/ml Cotinine in Plasma: 2.04 ng/ml Cotinine in saliva: 2.48 ng/ml Cotinine in urine: 7.71 ng/ml	Russel 1987
- Smokers	94	Nicotine in plasma: 14.8 ng/ml Nicotine in urine: 1749.9 ng/ml Cotinine in plasma: 275.2 ng/ml Cotinine in saliva: 309.9 ng/ml Cotinine in urine: 1391.0 ng/ml	
Staff			
- Clerical staff not exposed	20	Cotinine in plasma: 5.2 ± 1.5 ng/ml Cotinine inurine : 8.3 ± 6.7 ng/ml	
- Waiters, Waitresses exposed	26	Cotinine in plasma: 10.0 ± 4.0 ng/ml Cotinine in urine: 56 ± 37 ng/ml	Husgafvel - Pusiainen et al. 1987
- Smokers	22	Cotinine in plasma: 246 ± 91 ng/ml Cotinine in urine: 1578 ± 765 ng/ml	

Table 2: Nicotine and cotinine in body fluids of non-smokers and not exposed to tobacco under real conditions

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Groups studied/Exposure	N	Result			Literature
Clinical Staff					
- not exposed (a.m.)	30	Nicotine in urine:	7.5 ±	8.3 ng/ml	Feyerabend et al 1982
- exposed (a.m.)	26	Nicotine in urine:	21.6 ±	28.8 ng/ml	
- cigarette smokers (average inhalers)	32	Nicotine in urine:	1343.4 ±	1699.8 ng/ml	
Patients and Clinical Staff					
- not exposed	22	Cotinine in urine:	2.0 ng/ml (Median)		
- exposed	199	Cotinine in urine:	6.0 ng/ml (Median)		
- Cigarette smokers	131	Cotinine in urine	1645.0 ng/ml (Median)		Wald et al. 1984
Husbands					
- non-smoking wife	101	Cotinine in urine:	8.5 ±	1.3 ng/ml	Wald and Ritchie 1984
- smoking wife	20	Cotinine in urine:	25.2 ±	14.8 ng/ml	
Clerical Staff					
Blood samples at 11.30 and 19.45 (in between, two hours in a smoke-filled bar)	7		11.30	19.45	
		Nicotine in Plasma	0.8	2.5 ng/ml	
		Nicotine in urine	10.5	92.6 ng/ml	
		Cotinine in Plasma	1.1	7.3 ng/ml	Jarvis et al. 1983
		Cotinine in Saliva	1.5	8.0 ng/ml	
		Cotinine in urine	4.8	12.9 ng/ml	
Ambulant patients					
- non-smokers, not exposed	46	Nicotine in plasma:	1.04 ng/ml		
		Nicotine in urine :	3.87 ng/ml		
		Cotinine in plasma:	0.82 ng/ml		
		Cotinine in saliva:	0.73 ng/ml		Jarvis et al. 1984
		Cotinine in urine:	1.55 ng/ml		
- non-smokers, exposed	54	Nicotine in plasma:	0.77 ng/ml		Russel 1987
		Nicotine in urine:	12.11 ng/ml		
		Cotinine in Plasma:	2.04 ng/ml		
		Cotinine in saliva:	2.48 ng/ml		
		Cotinine in urine:	7.71 ng/ml		
- Smokers	94	Nicotine in plasma:	14.8 ng/ml		
		Nicotine in urine:	1749.9 ng/ml		
		Cotinine in plasma:	275.2 ng/ml		
		Cotinine in saliva:	309.9 ng/ml		
		Cotinine in urine:	1391.0 ng/ml		

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Staff				
- Clerical staff not exposed	20	Cotinine in plasma: 5.2 ± 1.5 ng/ml Cotinine inurine : 8.3 ± 6.7 ng/ml		
- Waiters, Waitresses exposed	26	Cotinine in plasma: 10.0 ± 4.0 ng/ml Cotinine in urine: 56 ± 37 ng/ml		Husgafvel - Pusiainen et al. 1987
- Smokers	22	Cotinine in plasma: 246 ± 91 ng/ml Cotinine in urine: 1578 ± 765 ng/ml		

Table 2: Nicotine and cotinine in body fluids of non-smokers and not exposed to tobacco under real conditions

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According to a study carried out by the Bremen Institute for Preventive Research and Social Medecine we must assume that the total exposure of non-smokers lies in the private sphere to more than 60%, the main cause being smoking spouses. However, in working men and women exposure at the place of work also plays an important part. According to a study by Letzel and Johnson the daily exposure to tobacco smoke amounts to between 1 to 2 hours for men and a little less for women. The duration of exposure fluctuates according to age and sex.

Epidemiological Findings - Lung Function in Adults

To date eight epidemiological studies are available, of which four point to a deterioration of lung function as a result of passive smoking. One of them is the paper by White and Froeb referred to earlier on, which does not attain scientific standards but is nevertheless the one most frequently quoted as evidence of lung damage through passive smoking. In the four other studies, including one from the Federal Republic, no influence of passive smoking on lung function was found. The problem with studies of this kind is that there are numerous environmental factors which can impair lung function and that it is difficult or even impossible to isolate one single cause. This is the view also taken in the 1986 Report of the Federal Environment Office.

Lung Function in Children

There exist at least twenty epidemiological studies, all carried out in a similar manner, in which the influence of parental smoking on the lung function of children is examined. Thirteen of them conclude that smoking by parents, especially by mothers, impairs the children's lung function. The differences between such children and others whose parents did not smoke were small and varied between less than 1% and 8%. In an analysis presented on the occasion of the "Indoor Air Conference '87" in Berlin, Professor Witorsch of the Virginia Commonwealth University (USA) doubted even this order of magnitude. He pointed out that in all these studies the socio-economic status of the parents and their children had been either left out of account altogether, or had been only very superficially taken into consideration. The socio-economic status however is related to smoking as well as to other factors which influence the measurement of children's lung function. Some of these are different attitudes to learning and an absence of motivation, which can have a negative effect on the test result. Moreover it is known that, as compared with non-smokers, smokers inhabit on the whole a lower socio-economic status which implies less favourable housing so far as area, size and equipment of accommodation are concerned, and with a less health-conscious life-style of the family with regard to nutrition, sports and other habits and

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attitudes. Here again it is virtually impossible in a statistical analysis to exclude all these 'confounding factors' as potentially contributory causes for a deterioration in the lung function and the appearance of pulmonary symptoms. In fairness it ought therefore to be conceded that the question as to the extent to which passive smoking plays a part in all this has not yet been satisfactorily answered. The suspicion however remains.

Coronary Heart Diseases

So far a total of 7 epidemiological studies are known which deal with the possible influence of passive smoking in the genesis of coronary heart diseases. In his above-mentioned study Hirayama found that in non-smoking wives of smokers of more than 20 cigarettes per day, there was a relative risk of 1.35. He did not, however, standardise other coronary risk factors such as hypertension or hyper-cholesterol-aemia. His observation is the more astonishing as in Japan smoking as such is of only limited significance for coronary heart disease. Garland and collaborators carried out a case-control study on wives of smokers and ex-smokers and established a relative risk of 2.7, which is marginally significant. Not to mention a few methodological problems which arise from this study, it is most remarkable that 15 of the 19 deaths were of wives of ex-smokers. This contradicts the findings relating to smokers, whose relative risk after giving up smoking declines rapidly and after a few years becomes the same as that of non-smokers. Three of the remaining studies tend towards establishing a link between passive smoking and coronary heart disease; two, including that by Garfinkel which is comparable to that by Hirayama, do not do so. The value of this study is doubted even in the mainly politically-motivated report of the American Surgeon General. Too many problems of method seem unanswered and the doubts concerning the plausibility of the results obtained so far are evident. The risk of death through a myocardial infarct is two to three times higher in our Western societies for smokers than for non-smokers.

It seems that smoking combines with other existing risk factors rather than being an independent risk factor itself. Nicotine and carbon monoxide which in theory are supposed to be responsible for the increased coronary risk to smokers cannot be potential causes as passive smokers absorb them only to a very small extent. This being so, Professor Schmähle was right when on one occasion he asked what could be the 'devilish substance' in tobacco smoke which could bring about such an increased coronary risk in indoor air.

Lung Cancer

In at least eight cohort-studies and 50 case-control studies a significant correlation was established between smoking and lung cancer. The relative risk of lung cancer to male smokers

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of one to ten cigarettes per day covers a span from 1.9 to 4.6. Where more than 25 cigarettes are smoked it rises to between 4.6 and 25.1. Since indoor tobacco smoke also contains mutagenic and carcinogenic substances -- though in much smaller quantities than in the mainstream smoke inhaled by the smoker -- the question whether passive smoking may bring about an increase in the risk of lung cancer is perfectly legitimate. As in the case of smoking, epidemiological studies are the proper means to discover any link that may exist. But because the risk to be expected is much smaller, these studies must be planned and carried out as faultlessly as possible. Otherwise we are likely to get artefacts rather than results.

So far three cohort studies are available, of which one does not permit any conclusion to be drawn because of the small number of cases: only six non-smoking men and eight non-smoking women. The American paper by Garfinkel does not present any link between passive smoking and lung cancer. In contrast, Hirayama believes, in the paper already referred to, that he can prove the existence of a significant dose-response ratio. Because mass studies are much superior to case control studies so far as the force of their evidence is concerned, and because Hirayama's findings have so far provided the strongest arguments in favour of a cancer risk through passive smoking, I should like to take a closer look at his work. At a symposium a few weeks ago in Tokyo, Professor Uberla, a former chairman of the Federal Health Office pointed out the following shortcomings of the paper in the presence of Dr. Hirayama:

- The paper was not planned in order to test the hypothesis that passive smoking is, or is not, associated with lung cancer;

- The group examined was not representative of Japan so that there may have been a bias in selection;

- The indicator for exposure to passive smoking -- being married to a smoking husband -- is neither reliable nor valid and it is not specific;

- The indicator for the potential consequences of passive smoking -- lung cancer as the cause of death in the death certificate -- is neither reliable nor valid;

- Various 'confounding factors' such as exposure at place of work, general air pollution, differences in nutrition, the type of medical treatment, etc., were not taken into account;

- A possible bias in the classification of women as non-smokers was not excluded, so that it may be assumed that there were some smokers amongst the non-smokers;

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- Almost nothing is known about the 200 deaths reported. There is not a single medical history available and histological findings and reports on autopsies are available in only 11.5% of the cases.

In their re-analysis of Hirayama's data, Uberla and Ahlborn found that the conclusions drawn by Hirayama on the basis of the data published so far are not cogent. When adjusted to the normal age-distribution in Japan the risk of lung cancer due to passive smoking disappeared altogether. In his address in Tokyo, Professor Kilpatrick of the Virginia Commonwealth University (USA) unreservedly agreed with this assessment.

Apart from the cohort studies we now have 19 case control studies. The great majority of these find a relative risk of > 1.0 for lung cancer through passive smoking. The risk-increase which reaches a maximum of 3.23 is significant in only a small number of studies, and a dose/response ratio is established only rarely. Case control studies in which relative risks of 2 or less, i.e. low risk associations, are to be discovered must be faultlessly planned and carried out if they are to allow any conclusion to be drawn at all. Otherwise an increased risk found could be due to a bias or confounding factor. It does not really matter whether such a risk increase is significant or not. After all, significance is no more than a yardstick for the probability of the fortuitously obtained figure being really different from the one expected, it being assumed a priori that the classification of cases is not governed by additional factors.

The first Report by the American Surgeon General, the 1964 Terry-Report, describes the criteria to be met by epidemiological studies in order that a causal link may be assumed. In his review paper "Lung Cancer from Passive Smoking: Hypothesis or Convincing Evidence?" just recently published in the 'International Archives of Occupational and Environmental Health', Professor Uberla notes that in the epidemiological studies published so far these criteria have not, or only partly, been met. A similar conclusion was arrived at by Professor Wynder of the New York American Health Foundation in his address in Tokyo a few weeks ago. The following must be taken into consideration when a causal link is examined:

- At a relative risk of <3 or even <2 the strength of the association is small in all studies. Therefore it would have been particularly important carefully to avoid possible mistakes of method, which was certainly not done. On the other hand there can be no doubt that even a slightly increased risk, if real, would be of great importance from the point of view of public health, given the widespread phenomenon of passive smoking.

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- As to the concordance of results within a study or between studies, many questions remain unanswered. Thus not all studies establish a link between passive smoking and lung cancer. In some cases such a link can be shown only through an analysis of sub-groups. In some studies the adenocarcinoma-rate only seems to have increased whereas in others it is only the rate of epithelium-carcinoma.

- Nor is the specificity of association, apparent in the relationship between the exposure and its consequences, properly assured. Neither the measure of exposure -- usually obtained by asking about the spouse's smoking habits -- nor the diagnosis of lung cancer are valid or specific in the light of available experience. In the light of Garfinkel's case-control study Wynder showed how difficult it is to carry out questioning correctly. If the questions were answered by the patient himself, the relative risk came to 1.0, if the spouse answered, it was 0.92, and if the replies came from either daughter or son the figure was 3.19, and when acquaintances were asked, it dropped to 0.77. Despite all these contradictions Garfinkel's study is regarded by some as a further proof of the risk of lung cancer through passive smoking because of its overall significantly-increased relative risk of 2.1. In fact however, in view of the problems highlighted, it would rather seem to prove the opposite. According to Lee the possibility of misclassification constitutes the greatest problem for epidemiological studies of passive smoking, and especially for case control studies. Misclassification quite simply has its origin in wishful thinking to which patients, relatives and researchers may be prone. Because of the human need to find a cause for a blow of fate the former tend to overestimate passive smoking as a possible cause, and the latter would like to see a preconceived opinion confirmed. Garfinkel and collaborators in fact point to the possibility of misclassification after they were compelled to find that about 40% of all patients registered as non-smokers in their sick-reports were in fact smokers. Lee calculated that a small percentage of women smokers erroneously classified as non-smokers was sufficient to falsify results and to show an increased risk of lung cancer through passive smoking.

- Problems arise with regard to time relationships. Though all epidemiological studies show that differing periods of latency precede the genesis of lung cancer due to exposure to passive smoking. But there is hardly one study in which passive smoking during childhood or youth has been properly taken into account. Since according to Doll and Peto the period of exposure in terms of life-years seems to be more important than the magnitude of the dose, passive smoking extending from childhood through adolescence into adult age is supposed to be particularly

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disadvantageous. Only Correa and collaborators made an effort to cover childhood smoking. They found that the relative risk of lung cancer was 1.0 where the father smoked and 1.66 where the mother did. This increased risk was significant only for male patients and did not apply to female patients. A further argument against the importance of passive smoking as a cause of lung cancer is proferred by Wynder: the risk of lung cancer in non-smokers should in fact have risen over the past decades in parallel with the greater frequency of lung cancer in smokers if passive smoking were a causal factor. This is however not the case.

- In some studies a significant dose/response ratio was found, such as in the cohort study by Hirayama and in the Greek case control study by Trichopoulos. But Uberla describes this latter as a text-book example for all those mistakes which should be avoided at all cost in a case control study. There are several studies in which there is no pointer to a dose/response ratio.

- The case for biological plausibility is similar to that of the epidemiological findings. In both cases there is more than enough reason for doubt. First, one may well wonder whether a fraction of the substances inhaled by smokers can really trigger off a relatively high risk of lung cancer through passive smoking. Epithelium carcinoma (Plattenepithelkarzinom) which according to some studies is supposed to be more than normally frequent in passive smokers begins in cilia-bearing cells which must have undergone metaplastic change. Auerbach and collaborators have shown that the preliminary stages of malignant changes in the bronchial tracts of passive smokers, namely metaplasia and dysplasia can hardly be proved and that the cilia of the cells seem to remain intact. It is likely that no preliminary stages of bronchial carcinoma can be detected because passive smoking does not overload the physiological defence system of the lungs. There is much that argues in favour of this view. It is, however, not proved.

  Since 1986 one particular form of evaluating epidemiological studies on passive smoking has gained great importance: it is known as meta-analysis and amounts to the merging of all - or at least most - presently available studies for the purpose of increasing the number of cases and thereby to arrive at a more reliable conclusion. The first analysis of this nature led Professor Wald of St. Bartholomew's Hospital, London, to conclude that the relative risk of lung cancer for passive smoking is 1.30 and thus significantly increased. Wald's paper was regarded as proof of the risk of lung cancer to passive smokers by both the American Surgeon General and the National Academy of Sciences. Despite the esteem in which the authorities hold that paper there are

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considerable doubts as to whether it is justifiable to merge the results of epidemiological studies of different quality and to evaluate them jointly. At the end of the day the conclusive value of a meta-analysis very clearly declines with the number and magnitude of the errors contained in the studies upon which it is based. Bearing this in mind, Letzel and Uberla carried out a further meta-analysis based only on those epidemiological studies which meet minimal standards of scientific quality. On the basis of twelve relevant studies they reached the conclusion that if the Trichopoulos-study is taken into account the relative risk amounts to 1.12, and if it is not, the figure declines to 1.08. That risk-increase however is not significant and remains within the limits of 'statistical smoking'.

Toxicology of Passive Smoking

In view of the evident difficulties epidemiologists encounter in helping to find out whether there is a link between passive smoking and lung cancer, it is not to be wondered at that the toxicologists have been giving more and more attention to the subject. The findings established so far were discussed in 1986 at a symposium in Essen and in 1987 at congresses in Berlin and Tokyo. The results, most of which were obtained in more or less controlled chamber-experiments are in part contradictory. Persons exposed to tobacco smoke most frequently complain about irritation of the mucus membranes, for which mainly substances contained in the gaseous phase, but probably also in the particle phase, are responsible. Subjective sensations of feeling ill and bad smell are quoted as additional nuisances. According to Professor Winneke of the Institute for Air Hygiene and Silicosis Research of Düsseldorf University early difficulties of this nature occur when the concentration of tobacco smoke corresponds to 5 ppm CO and not, as alleged in an earlier study by Weber and collaborators, at 2 ppm CO. Whereas irritations increase with the duration exposure, the other effects are complained of only during the initial ten to fifteen minutes.

Nicotine, cotinine and thiocyanate in body fluids as well as carboxyhaemoglobin merely show that there has been exposure to tobacco smoke. In order to cover the long-term effects of exposure to tobacco smoke it would seem necessary to examine the absorption and the effect of compounds with genotoxic qualities. Below, the results are presented of a number of experiments which deal with this problem.

Phenanthrene is part of the group of polycyclic carbohydrates (PAH) and is contained in cigarette smoke, diesel exhaust fumes and also in roast pork. Hydroxyphenanthrenes are products of the metabolism of phenanthrene and are rightly considered to be

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markers for the absorption of PAH. We were able to show that the excretion of hydroxyphenanthrene in urine does not increase after an 8-hour exposure to tobacco smoke, irrespective of whether the concentration at 10 ppm CO is medium or very high at 20 to 25 ppm CO. (Graph 1). The excretion of hydroxyphenanthrene changes significantly if, after a diet low in PAH, one is provided which is high in PAH. Extremely high excretion of hydroxyphenanthrene is found in workers exposed to high PAH concentrations at work. Data established in co-operation with Professor Grimmer from the Biochemical Institute for Environmental cancer in Hamburg show how widely the PAH impact fluctuates and how secondary the role which passive smoking plays therein.

Mercapturic acids (thioethers) are the detoxification products of many electrophile, and thus potentially mutagenic and carcinogenic, substances. Their genesis is catalysed by the glutathion-S-transferase-system and their rate of excretion in urine can be used to measure the impact of these compounds. The excretion of mercapturic acids rises slightly when a non-smoker has been exposed for 8 hours to a tobacco smoke concentration of 10 ppm CO and increases further when this is doubled (Graph 2). As compared with non-smokers, the thioether-excretion is still higher than normal in smokers after an abstinence of 36 hours and, after ten to 20 cigarettes have been smoked, it increases more vigorously than in passive smokers. The higher excretion of thioethers after passive smoking was, by the way, described for the first time and was probably discovered only because the diet of the test persons had been strictly controlled over a period of several days. The results of the experiment carried out in co-operation with Professor Sorsa of the Institute of Occupational Health in Helsinki confirm the view that through passive smoking electrophile substances are absorbed and detoxified. How effective this detoxification is, requires further study.

Mutagenic and carcinogenic substances are excreted in urine if they neither react with macromolecules in the organism, such as DNA, nor are detoxified in metabolism through the various protective enzyme systems. They can be detected in urine through the Ames-Test. In our experiment we found no significant increase in mutagenic activity in passive smokers either after a medium (10 ppm CO) or a high eight-hour exposure to tobacco smoke (20 to 25 ppm CO) (Graph 3). With one exception our results agree with those of other authors so far as the extent of mutagenic activity is concerned. Professor Norpoth's working party of the Institute of Hygiene and Social Medecine of Essen University found an increase in passive smokers which corresponded to that of smokers of four to five cigarettes. The reason for this different result is not at present known and needs to be discovered. Our results suggest that in contrast to smoking, passive smoking leads to the absorption of too few mutagenic or carcinogenic substances for

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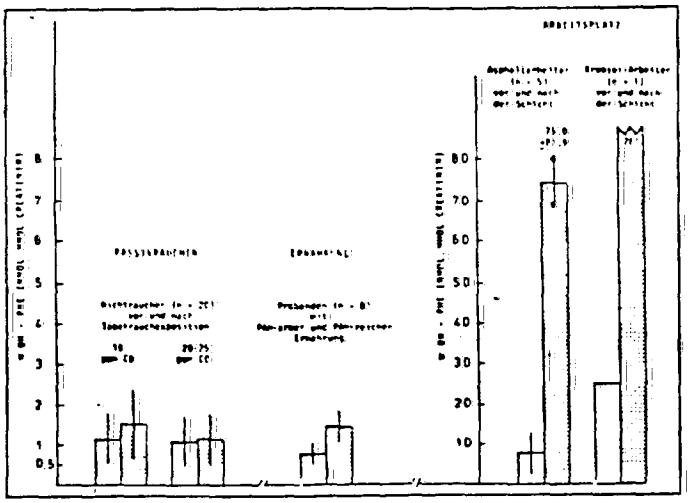
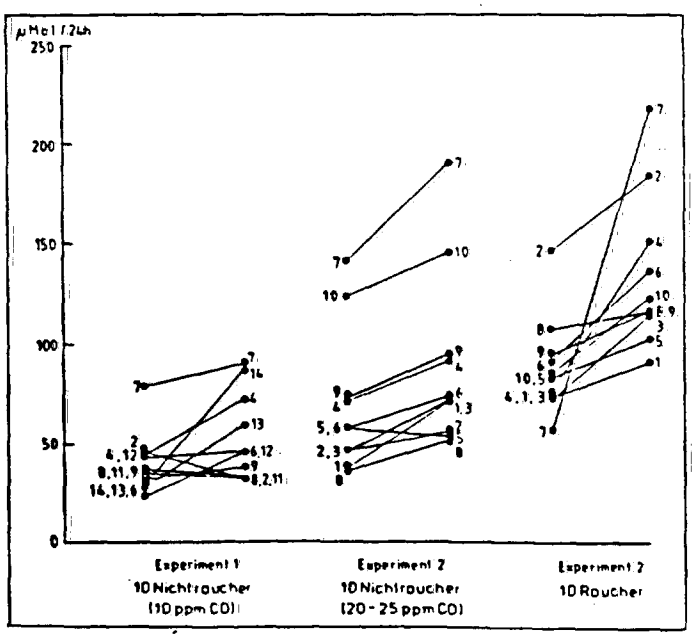


Graph 1

Hydroxyphenanthrene excretion in urine following PAH absorption during medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, during nutrition both poor and rich in PAH and at selected workplaces.



Graph 2

Thioether excretion in the urine of non-smokers before and after eight-hour-long medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, compared with that of smokers.

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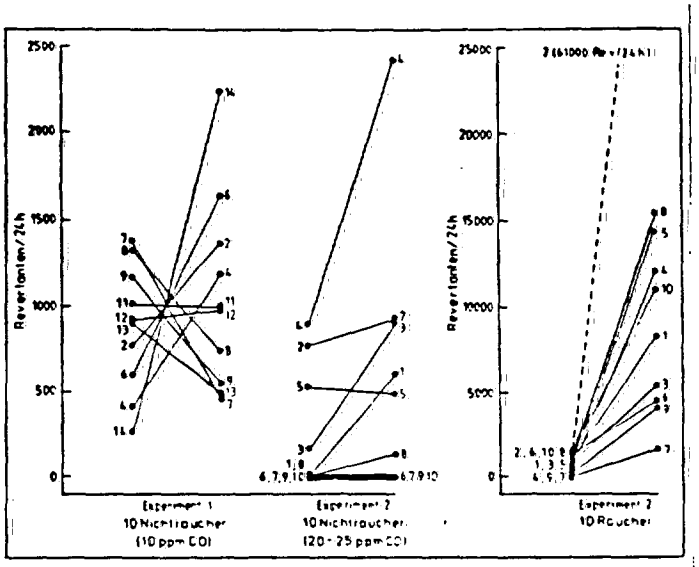

Graph 3

Mutagenic activity in the urine of non-smokers before and after eight-hour-long medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, compared with that of smokers.

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them to be detected with the Ames-Test in urine. It is however just as possible that these substances can be effectively detoxified in passive smokers through the cellular glutathion-S-transferase-system and other enzymes, which does not seem to be possible in the case of smokers because of the overload with which their metabolism is charged.

Under the impression of the results of the symposium on "Experimental Toxicology on Passive Smoking" in Essen Professor Gostomczyk made the following comment: "Taking into account the results of the Essen symposium we may say that toxicologists have so far no more than epidemiologists rendered more probable the existence of a link between passive smoking and injuries to health." Our findings should be interpreted on the same lines.

Conclusions

Tobacco smoke indoors contains toxic, mutagenic and carcinogenic substances which are inhaled by non-smokers. The concentrations are all low. There does not, at present, exist a marker for indoor tobacco smoke. The reason for this is that the composition of tobacco smoke differs according to the product from which stems, and that it is subject to constant quantitative and qualitative change through ageing. It is almost always mixed with substances of another origin, the concentration of which is frequently higher than that due to tobacco smoke. However, nicotine, which is specific to tobacco smoke, can be used to provide qualitative proof of indoor air pollution through tobacco smoke.

The particle phase of tobacco smoke is retained in the lungs at a rate of a little more than only 10% after inhalation. It may be assumed that a considerable part of it is not absorbed by the organism but is removed from the respiratory passages through the cleansing mechanism of the lungs. Reactive compounds of the gaseous phase and/or such which are easily soluble in water are largely resorbed in the nose and throat area and the upper respiratory passages. This is to some extent also true of nicotine, the metabolism of which varies from individual to individual, and is mainly broken down into cotinine. The presence of nicotine and cotinine in body fluids confirms exposure to tobacco smoke. It is hardly possible to quantify the impact of tobacco smoke on the basis of the nicotine or cotinine concentration in body fluids. Such a procedure is hampered by the great difference between indoor tobacco smoke and mainstream cigarette smoke, the quick quantitative and qualitative changes to which indoor tobacco smoke is subject, the specific physico-chemical qualities of nicotine, and the individual differences in the metabolism of nicotine. Carbon monoxide and thiocyanate are further, but unspecific, markers for the absorption of tobacco smoke.

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Epidemiological studied carried out so far and which point to a link between passive smoking and lung cancer as well as other diseases are tainted with so many errors - when critically considered - that they cannot be regarded as confirming any danger to health due to passive smoking. Problems in measuring exposure to tobacco smoke, in eliminating misleading factors such as misclassifications or 'confounders', and in the diagnosis and typification of lung cancers, have on the whole not been resolved. In the opinion of many scientists the epidemiological methods available to-day are probably inadequate to discern any risk to health through passive smoking, if indeed there is such a risk.

Since epidemiology has so clearly failed to establish whether there is a risk to health through passive smoking, it is not to be wondered at that by now toxicologists have taken the matter up. At present they are the strongest upholders of the theory of harmfulness to health, especially of the danger of cancer through passive smoking. They rightly assume that through passive smoking mutagenic and carcinogenic substances are inhaled, albeit in weak concentrations. They further assume, probably wrongly, that there is no threshold for cancerogenic substances, right down to the single molecule. These two assumptions together of necessity lead them to the conclusion that the risk of lung cancer - and probably of other cancers too - is increased through passive smoking, however small that increase may be. A linear extrapolation from tobacco-pollution through smoking to tobacco-pollution through passive smoking, which is made as a result of these assumptions and does not seem justified in the light of the known facts, leads to a similar assessment.

The question whether passive smoking causes lung cancer becomes the more of a political problem the more it is emotionalised in public discussion and the less science is able to provide an answer. For the present we can only say that danger to health is theoretically a possibility but has by no means been scientifically proved. Politicians interested in health affairs want to know whether a risk to health is probable. My answer would be "No", but I realise that we may yet have to wait a long time for the final word.

Literature can be obtained from the author.

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PASSIVE SMOKING AND LUNG CANCER: REANALYSES OF HIRAYAMAS DATA

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ABSTRACT

The cohort investigated by HIRAYAMA has a serve selection bias by age. The effect of removing this selection bias by iterative proportional fitting a contingency table to given marginals is investigated. The risk increase reported by HIRAYAMA disappears completely when one removes selection bias by age. If the cases would have been observed as they occur in the female population one would have observed no risk increase. Only in the subgroup of women married to industry workers there remains a risk increase, which might be due to confounding factors. Assuming modest differential misclassification also leads to risk ratios around unity.

INTRODUCTION

The statistical association between enviromental tobacco smoke and lung cancer is controversial. The HIRAYAMA study seems to provide sound epidemiological evidence supporting this hypothesis. In a recent paper ÜBERLA (6) has analysed the published studies. Regarding the HIRAYAMA study the following facts have to be kept in mind:

- The study was not designed to test the hypothesis, whether passive smoking is associated with lung cancer or not. It can therefore only generate this hypothesis, not prove it.
- The cohort was not representative for the population of Japan. A selection bias is possible.
- The exposure indicator - the fact of being married to a man who smokes - is not reliable, not valid and not specific.
- The event indicator - dying on lung cancer as noted on death certificates - is neither reliable nor valid.
- Various confounding factors - for instance exposure at the working place, indoor air pollution, overall air pollution, type of medical care - were not accounted for.
- Bias in registering the fact, that a woman is a nonsmoker, was not controlled. Resulting differential misclassifications of the cases, who were smokers and had to be excluded, have not been considered.
- Almost nothing is known about the 200 cases. No case reports are available, autopsy and histology are only available in 11.5 %.

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The core of the information, on which the results of this study rely, is

1.) that during 1965 200 women in Japan told an interviewer on a single occasion that they were - during that time - non-smokers and their husbands told, that they were smokers, which might have been different before and afterwards and
2.) that their death certificates subsequently contained the diagnosis lung cancer, which might have been erroneous.

Such sparse information does not seem to be convincing.

In our paper we consider four questions:
1.) What is the relative risk when one removes the selection bias regarding age of women in the HIRAYAMA cohort?
2.) What is the relative risk when one additionally accounts for the fact that women above 70 who are married to husbands still living are less frequent than reported in the population statistic?
3.) What is the relative risk for women married to men with different occupations, when one removes the selection bias regarding age of men?
4.) What is the relative risk when additionally some modest differential misclassification is assumed?

MATERIALS AND METHODS

We start from tables 1, 2 and 3 of HIRAYAMA 1984 (4). These tables contain the most detailed published data. In order to check our program we reproduced some of the reported relative risks with good accuracy.

PERCENT FEMALE

AGE GROUP	JAPAN POPULATION	HIRAYAMA COHORT
40-49	39	42
50-59	30	35 ↑
60-69	19	22
70+	12	1 ↓
	100	100

TABLE 1: Differences between the HIRAYAMA cohort and the female age distribution over 40 in the population of JAPAN 1965 (Population census 1965. Statistical survey of the economy of Japan. 1967, Ministry of Foreign Affairs of Japan).

There are marked differences between the HIRAYAMA cohort and the female age distribution over 40 in the population of Japan 1965. Women 50-59 are over-represented, women older than 70 are severely underrepresented. In this age group only one percent was observed instead of 12 percent in the population. The investigated cohort certainly has a severe selection bias by age, which needs no statistical test. This is likely due to the fact, that the smoking behaviour was not known in the elderly or that the husbands of older women have died. Since it takes twenty years and more from exposure to lung cancer, older women surely are relevant and should not be excluded. The majority of lung cancer cases occur in older age groups, in Germany more than 67 % in women over 65 years.

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In order to answer the question what the relative risk is when the age selection bias is removed, we adjusted the data to the age distribution of the female population of Japan. The technique of iterative proportional fitting a contingency table to given marginals as described by BISHOP, FIENBERG and HOLLAND (1) or by HARTUNG (3) was used. This technique keeps the risks constant as observed in every cell and changes the marginals and the cell counts according to the given age distribution of the population. Iterative proportional fitting of contingency tables to given marginals is a well known technique in multivariate statistics and can be applied here without changing the observed interrelations between smoking habit, occupation and lung cancer. From the fitted or adjusted tables the risk ratios are calculated in the usual way. Such risk ratios based on data with removed age selection bias are the correct ones and should be used. One has to require that there should be no selection bias by age and the cases should be included as they would have occured in the population. Otherwise statistical tests and P-values are not very meaningful.

WIVES AGE	HUSBAND'S SMOKING HABITS NON		1 - 19		20 +		TOTAL	
40-49	4	7918	21	17492	21	12615	46	38025
50-59	14	7635	46	15640	31	8814	91	32089
60-69	16	6170	31	10381	10	3793	57	20344
70 +	3	172	1	671	2	239	6	1082
TOTAL	37	21895	99	44184	64	25461	200	91540

TABLE 2: SMOKING HABIT OF HUSBAND BY AGE OF WIFE. ORIGINIAL DATA (Table 2 of HIRAYAMA 1984).

Table 2 shows the original data by age of wife. The cells contain the number of lung cancer cases and those under risk as published by HIRAYAMA. The 1-19 group includes ex-smokers in this and the following tables. 200 cases out of 91540 women were observed. Iterative proportional fitting to the female age distribution of the population leaves the underlined numbers constant. The others are adjusted using a rigth hand marginal which is made proportional to the age distribution of the population.

RESULTS

Table 3 gives the results of iterative proportional fitting to the female age distribution of the population. It contains the numbers of those under risk and of lung cancer deaths as they would have been ovserved, if HIRAYAMA had not excluded or preferred certain age groups. The age selection bias is removed. The risks in the individuall cells are still the same as those observed by HIRAYAMA. Also the structure of the common distribution regarding age, smoking habit and lung cancer is unchanged. HIRAYAMA would have totally observed 232 cases instead of 200, with the corresponding numbers in the individuall cells, had he included all women as they live in the population. This table is the best available starting point for age-adjusted risk ratio calculations. It was not used so far.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

WIVES AGE		NON		HUSBAND'S SMOKING HABITS 1 - 19		20 +		TOTAL	
40-49	3.91	7784.8	19.12	15927.8	20.02	12024.0	43.05	35700.6	
50-59	12.49	6813.7	38.20	12987.1	26.95	7661.2	77.64	27462.0	
60-69	14.25	5496.6	25.70	8604.9	8.68	3291.1	48.63	17392.6	
70 +	32.02	1835.2	9.93	6664.2	20.79	2484.7	62.74	10984.8	
TOTAL	62.67	21895	92.95	44184	76.44	25461	232.06	91540	

TABLE 3: SMOKING HABIT OF HUSBAND BY AGE OF WIFE (Table 2 of HIRAYAMA 1984). Removed selection bias: Data adjusted to the age distribution of women in the population.

	HUSBAND'S SMOKING HABITS NON	1-19	20 +
$\hat{RR}$	1.00	1.37	1.56
IL_{90}		1.00	1.11
MH-CHI		1.51	2.27
$P_{ONE\ TAILED}$		.065	.012*
$\hat{RR}$	1.00	.77	1.06
IL_{90}		.59	.80
MH-CHI		2.19	.27
$P_{ONE\ TAILED}$		.014**	.395

UPPER PART : STANDARDIZED BY AGE OF WOMEN ONLY
LOWER PART : AGE SELECTION BIAS REMOVED AND STANDARDIZED BY AGE OF WOMEN

RR : Weighted point estimate of rate ratio
IL_{90} : Lower 90 percent confidence interval
* : "significant" in positive direction
** : "significant" in negative direction

TABLE 4: RELATIVE RISK BY AGE OF WOMEN (Calculated from table 2 of HIRAYAMA 1984).

In the upper part of table 4 one finds the risk ratios standardized by age only, as reported by HIRAYAMA. The lower part contains the risk ratios after removing the age selection bias. In the upper part the weighted point estimate of the rate ratio is 1.56 in the 20 + group and is technically "significant". IL_{90} designates the lower point of the 90-percent confidence interval in this and the following tables, as it was used by HIRAYAMA.

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The risk increase disappears completely when one removes the selection bias by age. In the 20 + group the rate ratio is 1.06, hardly a relevant risk increase. In the group of 1-19 cigarettes per day it is .77 which is a technically significant risk decrease. The adjusted rate ratio, considering all those exposed in one group versus those not exposed is .81 with a confidence interval including unity. If HIRAYAMA had observed the cases as they occur in the population without selection bias by age, he would have observed no risk increase, but a sligth and meaningless risk decrease. This is the main result of our reanalysis, which corresponds well with the result of the prospective American cohort study as published by GARFINKEL (2).

In the discussion following our paper in TOKIO last november HIRAYAMA noted, that in the population the percentage of women over 70 married to men who are still alive is smaller than the percentage of women reported in the population statistics. Since we do not have the numbers we assume that only half of the women over 70 reported in the population census 1965 have been married to living husbands. The resulting hypothetical population together with the HIRAYAMA cohort is presented in table 5.

AGE GROUP	PERCENT FEMALE HYPOTHETIC POPULATION	HIRAYAMA COHORT
40-49	42	42
50-59	32	35 ↑
60-69	20	22
70 +	6	1 ↓
	100	100

TABLE 5: DIFFERENCES BETWEEN THE HIRAYAMA COHORT AND A HYPOTHETIC FEMALE AGE DISTRIBUTION OVER 40. (Explanation see text)

There is still possibly a selection bias in table 5. Now 6 percent of women over 70 would have been included in the hypothetic female distribution instead of 12 percent. The corresponding lung cancer cass, which generally are more frequent in this age group than in younger women, had been excluded. The reduction to one half accounts for the argument of HIRAYAMA mentioned above sufficiently. The resulting relative risks are presented in table 6. Even with these assumptions the relative risk is only 1.03 in the group of women married to husbands smoking 1-19 cigarettes per day, 1.29 in the 20 + group and 1.12 if one considers the smoking group altogether. All these risk ratios are not statistically different from unity.

	HUSBAND'S SMOKING HABITS NON	1-19	20 +	SMOKER
$\hat{RR}$	1.00	1.03	1.29	1.12
IL_{90}		.77	.94	.85
MH-CHI		.05	1.33	.47

TABLE 6: RELATIVE RISK BY AGE OF WOMEN, AGE SELECTION BIAS REMOVED AND HYPOTHETICALLY ADJUSTED TO HIRAYAMAS ARGUMENT (see table 5)

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Since it is impossible for us to reconstruct the real situation some twenty years ago in Japan regarding the conditional distributions of males and females regarding age, smoking and family status, the reported results of the HIRAYAMA study can not be conclusive to us. As long as the selection bias by age can not be explained numerically in a sufficient way by HIRAYAMA, his thesis, that there is a significant and relevant risk increase based on his data migth as well be wrong.

We now consider two occupations, farmers and industry workers. From the upper part of table 7 one can see that the relative risk for wives of farmers seems substantial, when one standardizes by age of men only. The point estimates of the rate ratios are 1.48 and 1.63 respectively. This was observed earlier and had no adequate exlanation. If one removes the selection bias by age and adjusts to the male age distribution of Japan - the numbers in the lower part of table 7 - the rate ratios are .85 and .82, not different from unity. This seems more plausible.

	HUSBAND'S SMOKING HABITS		
	NON	1-19	20 +
$\hat{RR}$	1.00	1.48	1.63
IL_{90}		.97	1.01
MH-CHI		1.48	1.92
$P_{ONE\ TAILED}$		.069	.027
$\hat{RR}$	1.00	.85	.82
IL_{90}		.59	.53
MH-CHI		.42	.53
$P_{ONE\ TAILED}$		.337	.296

UPPER PART : STANDARDIZED BY AGE OF MEN ONLY
LOWER PART : AGE SELECTION BIAS REMOVED AND STANDARDIZED BY AGE OF MEN

TABLE 7: RELATIVE RISKS: WIVES OF FARMERS ONLY
(Table 3 of HIRAYAMA 1984)

Considering the wives of industry workers only, in the upper part of table 8 the point estimates of the rate ratios are 1.77 and 2.27, standardized by age of men, being not significant. Removing the age selection bias - in the lower part of table 8 - there is a remarkable risk increase to 4.60 and 6.90, which is significant. However, there are only 9 lung cancer deaths in the 20+ group and only 3 in women 70 years and older, which are small numbers, but these are numbers observed and used by HIRAYAMA and his risk structure is unchanged. Thus only in the subgroup of women married to industry workers there is a risk increase, in all other occupations there is no risk increase. Omitting industry workers, the point estimates of the rate ratios are .90 and .89, not significantly different from unity. These findings are consistent with the assumption of confounding factors in women married to industry workers, who migth be exposed to other enviromental hazards. Our calculations show that by removing age selection bias by age, one can explain hitherto implausible results.

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	HUSBAND'S SMOKING HABITS NON	1-19	20 +
$\hat{RR}$	1.00	1.77	2.27
IL_{90}		.70	.84
MH-CHI		.73	.81
$P_{ONE\ TAILED}$		.232	.208
$\hat{RR}$	1.00	4.60	6.90
IL_{90}		1.71	2.45
MH-CHI		2.50	2.78
$P_{ONE\ TAILED}$		.006	.003

UPPER PART : STANDARDIZED BY AGE OF MEN ONLY
LOWER PART : AGE SELECTION BIAS REMOVED AND STANDARDIZED BY AGE OF MEN

TABLE 8: RELATIVE RISKS: WIVES OF INDUSTRY WORKERS ONLY
(Table 3 of HIRAYAMA 1984)

Active smoking is correlated among married couples. In a society in which female smokers were very rare in 1965, more women married to smokers will declare themselves nonsmokers than the other way round. One has therefore to consider biased or differential misclassification. There are likely more women with lung cancer, who have been misclassified as nonsmokers than the other way round. They have to be removed from the cohort. We made some moderate assumptions regarding misclassification, as shown in table 9. In order to examine, how sensitive the relative risk is we removed 10, 20 and 30 cases from the exposed groups corresponding to 5, 10 and 15 percent. Assuming 30 misclassified cases - 15 percent, a percentage which has been observed in the literature (5) - the rate ratios are .66 and .85. In the group 1-19 cigarettes per day all the risk estimators are significantly smaller than unity. Our personal opinion is that 10 differential misclassified cases from 200 is a fair number. The corresponding weigthed point estimates of the rate ratio are .74 and 1.00. These risk estimates are as reasonable as other risk estimates calculated from the HIRAYAMA data. They indicate - if anything - a risk decrease, not a risk increase.

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NUMBER OF CASES ASSUMED MISCLASSIFIED AND REMOVED FROM EXPOSED GROUPS		HUSBAND'S SMOKING HABITS		
		NON	1-19	20 +
n = 10 = 5 %	$\hat{RR}$	1.00	.74	1.00
	$P_{ONE\ TAILED}$		.006	.469
n = 20 = 10 %	$\hat{RR}$	1.00	.70	.93
	$P_{ONE\ TAILED}$		.003	.383
n = 30 = 15 %	$\hat{RR}$	1.00	.66	.85
	$P_{ONE\ TAILED}$		.001	.238

TABLE 9: RELATIVE RISK: ASSUMED DIFFERENTIAL MISCLASSIFICATION
(Age selection bias removed and standardized by age of women)

DISCUSSION

Reanalyses of data, which have been collected by others are not easy. This is because information is not completely available, because information might be misinterpreted or because one has to take another view in order to come closer to the acceptable truth. Our calculations do not diminish the great value and impact the HIRAYAMA study had on the epidemiology of passive smoking. They show however, that reasonable alternative views on the same data are possible, which lead to opposite conclusions. Our findings are in contrast to HIRAYAMA's thesis that - based on his data - there is a substantial statistical association between passive smoking and lung cancer. We do not hold that our view is the only correct one. We do hold however, that the risk ratios calculated by us, removing age selection bias, are as reasonable as the ones calculated by HIRAYAMA. Since they go back to the population and not to a selected sample our estimates could be preferable. Hypothetically accounting for the argument of HIRAYAMA, that in the population the percentage of women over 70 married to men who are still alive is smaller than the percentage of women reported in the population statistics does not change our results. Our risk estimates are a consequence of the data published by HIRAYAMA and can not be rejected from the study data, as they are published so far.

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		HUSBAND'S SMOKING HABITS		
		NON	1-19	20 +
AGE SELECTION BIAS REMOVED AND AGE-STANDARDIZED (WOMEN)	$\hat{RR}$	1.00	.77	1.06
	$P_{ONE\ TAILED}$		.014	.395
WITHOUT INDUSTRY WORKERS, AGE SELECTION BIAS REMOVED AND AGE-STANDARDIZED (MEN)	$\hat{RR}$	1.00	.90	.89
	$P_{ONE\ TAILED}$		.394	.179
10 CASES ASSUMED MISCLASSIFIED, AGE SELECTION BIAS REMOVED AND AGE-STANDARDIZED (WOMEN)	$\hat{RR}$	1.00	.74	1.00
	$P_{ONE\ TAILED}$		.006	.469

TABLE 10: REANALYSIS OF HIRAYAMAS DATA: SUMMARY OF RELATIVE RISKS

To summarize: Removing the age selection bias in the HIRAYAMA study one gets a relative risk of 1.06 in the group of women married to men with more than 20 cigarettes per day. In the group of women married to men with 1-19 cigarettes per day the relative risk is .77, a technically "significant" risk decrease. If HIRAYAMA could have observed the lung cancer cases as they occur in the female population, he would have observed no risk increase, but a risk decrease to around .81, not significantly different from unity, considering those exposed versus those not exposed.

If one omits the wives married to industry workers because of possible confounding factors the relative risk is .90 and .89 respectively. This is of the same size order and smaller than unity. Here we could adjust and standardize by occupation and age of men only, which is not as appropriate as by age of women.

If one assumes that 10 cases are differentially misclassified and removes them from the exposed groups, the risk estimates are .74 and 1.00 respectively.

Our findings demonstrate how sensitive the data of this study are and how week the evidence for a statistical association between passive smoking and lung cancer from this study is. In view of these and other facts, which we mentioned in the introduction, the null hypothesis might be true as well and is consistent with the HIRAYAMA data in the same way as the alternative hypothesis.

We would be glad to apply our technique to more detailed data if we can get them from HIRAYAMA, for instance in order to adjust by occupation of men and age of women, or by occupation of men and by age of women married to a husband who is still alive. We are ready to modify our view if such data can support the alternative hypothesis better than the published data do. We do hope, that our calculations give rise to a fruitful discussion. The methods we used here might be of interest to the analysis of other cohort and control studies.

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References

1. Bishop YV, Frienberg StE, Holland PW
Discrete Multivariate Analysis: Theory and Practice
MIT Press, Cambridge p. 97 (1980)

2. Garfinkel L, Time trends in lung cancer mortality among nonsmokers and a note on passive smoking, J Natl Canc Inst 66 : 1061-1066 (1984)

3. Hartung J, Elpelt B, Klösener KH
Statistik. Lehr- und Handbuch der angewandten Statistik.
München - Wien - Oldenburg, pp. 501-503 (1985)

4. Hirayama T, Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P (eds.) Lung cancer: Causes and prevention. Verlag Chemie, Weinheim, pp. 175-195 (1984)

5. Lee PN, Chamberlain J, Alderson HR, Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br. J. Cancer 54: 97-105 (1986)

6. Überla K, Lung cancer from passive smoking: hypothesis or convincing evidence? Int Arch Occup Environ Health 59: 421-431 (1987)

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Meta-Analyses on Passive Smoking and Lung Cancer

H. Letzel and K. Überla

Summary

Up to now, meta-analysis has rarely been used in epidemiology and no generally accepted standards are available. Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers.

In our paper two cohort and ten case-control studies were analyzed using several statistical techniques (Fisher, Mantel-Haenszel, Yusuf). Only data from women were included and a quality indicator (histology exposure, methodology) was used to analyze different study combinations, i.e. an analysis of sensitivity was performed. For the Hirayama study two different risk estimates were used. In addition, all 1,023 logically possible combinations of the 10 case-control studies were analyzed.

Of all possible meta-analyses of the 10 case-control studies, 670 (65.5%) were not significant at $P \leqq 0.05$ (Yusuf technique). The Trichopoulos study is involved in 330 of the 353 significant study combinations, indicating that this is the dominating case-control study, although the methodological quality is unacceptable.

Combining case-control and cohort studies, the relative risk estimates range from 1.013 to 1.118, depending on the specific subset of studies analyzed. These relative risk estimates include unity. The quality of the individual studies is highly variable and sometimes poor. We conclude that as long as no better studies are available, meta-analyses cannot and do not add much new evidence to the question of whether passive smoking is related to lung cancer.

Up to now, meta-analyses have mainly been used with randomized clinical trials. The technique has been criticized [6, 10, 23] for various reasons. Standards for meta-analyses in epidemiology are not yet available. Bias by non-reporting of studies, by selecting certain subgroups or by redefining sample sizes can create additional difficulties for a statistical evaluation. How different study designs – e.g. case-control versus cohort studies – should be weighted is left to the investigator. It is not surprising that the application of such methods in a controversial field like passive smoking and lung cancer does not come up with uniform results.

The inclusion of studies in meta-analyses is justified as long as there are no major methodological shortcomings in the individual studies. Combining biased or confounded results by meta-analysis cannot provide correct answers. There is a strong case for an analysis of sensitivity [23]. It investigates the effect of different study selections as well as the impact of different statistical methods on the results.

When the first papers on passive smoking and lung cancer were published a serious hypothesis was created [11, 27]. This hypothesis is serious because – if it is right – thousands of non-smokers are being killed worldwide by smokers. But the hypothesis is also serious because – if it is wrong – smokers are being accused of killing other people without actually doing so.

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Last year Wald [31] published the first meta-analysis of the available studies on passive smoking and lung cancer. In his paper the results obtained in men were included, and in two studies the subgroup of women married to ex-smokers was excluded. The quality of the individual studies was not taken into account and no analysis of sensitivity was performed.

Every meta-analysis has to state its goals, criteria and methods before it starts. In our analysis we planned

1) to include only studies which fulfil minimal methodological requirements. We wanted to eliminate statistical noise.
2) to select carefully the "best" relative risk estimate from every study, not just the one which was reported by the authors or the highest one.
3) to classify the quality of the studies regarding determination of histology, estimation of exposure and overall study methodology.
4) to use different statistical techniques, namely the Fisher method and the method used by Yusuf [32] or Wald [31].
5) to study the sensitivity of the results with regard to including different subsets of studies depending on their qualities.

Selection of Studies

We did not include the studies by Gillis [9], Knoth [16], Miller [22] and Sandler [24–26]. These studies do not fulfil minimal methodological criteria and they do not contain relevant information. Only insufficient data are available from them. Wald [31] had included the Gillis study [9], which only has 14 non-smoking lung cancer cases and correspondingly wide confidence intervals contributing nothing to the available evidence.

We also excluded men because the majority of evidence comes from studies in women. Only about 11% of the reported cases are men. Their results vary widely. There is not a single significant result in men. The situation regarding biology, exposure and reporting habits is considerably different in men as compared to women.

We included two cohort studies [7, 12–14] and 10 case-control studies [1–5, 8, 15, 17, 19–21, 27, 28]. These studies had also been included by Wald [31]. The only difference is that we didn't include the Gillis study [9] and that we restricted our analysis to women. The availability of histology, the quality of the exposure indicator and an overall quality rating of the study were judged by K. Überla. Three study groups resulted: cohort studies, case-control studies with reasonable quality (quality +) and case-control studies with poor quality (quality −) (Table 1).

The 2 × 2 tables and RR estimates for the 12 studies used are presented in Table 2. Generally, these numbers are the same as used by Wald [31] with the exception that we did not exclude the wives of ex-smokers in the studies by Hirayama [14], Trichopoulos [27, 28] and Koo [17].

Regarding the Hirayama study we did not use a relative risk estimate of 1.63 as did Wald [31]. In a subsequent paper by Überla and Ahlborn [30], which will be presented in this session of the conference, it is shown that, when one adjusts the Hirayama cohort to the age of the female population in Japan, the relative risk is 0.90. We alternatively used a risk estimate of 1.45 for the Hirayama study. This was calculated from Table 2 of the 1984 publication by Hirayama [13] and was standardized by the age of women only.

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Table 1. Quality rating of studies selected for meta-analyses

Author	Histology	Exposure	Quality rating**	Resulting group
Hirayama	–*	–	3	Cohort
Garfinkel	–	–	2	Cohort
Chan et al.	+	+	4	CC quality +
Correa et al.	–	–	5	CC quality –
Trichopoulos et al.	–	–	6	CC quality –
Buffler et al.	+	–	4	CC quality +
Kabat et al.	+	+	4	CC quality +
Garfinkel et al.	+	+	4	CC quality +
Akiba et al.	–	–	5	CC quality –
Lee et al.	–	+	5	CC quality –
Koo et al.	+	+	4	CC quality +
Pershagen et al.	+	+	4	CC quality +

The included studies are the same as in the paper by Wald et al. (1986). We included women only.
** 2 = acceptable; 3 = possibly flawed; 4 = bias and confounding suspected; 5 = major bias and confounding suspected; 6 = unacceptable

Table 2. 2 × 2 Tables and relative risk estimates for studies selected for meta-analyses

Author	Exposed lung cancer		Unexposed lung cancer		Relative risk
	+	–	+	–	
Hirayama	163	69,428	37	21,858	1.45 (1) 0.90 (2)
Garfinkel	88	127,164	65	49,422	1.18
Chan et al.	34	66	50	73	0.75
Correa et al.	14	61	8	72	2.03
Trichopoulos et al.	53	116	24	109	2.01
Buffler et al.	33	164	8	32	0.80
Kabath et al.	13	15	11	10	0.79
Garfinkel et al.	91	254	43	148	1.23
Akiba et al.	73	188	21	82	1.48
Lee et al.	22	45	10	21	1.03
Koo et al.	66	97	22	40	
Pershagen et al.	33	150	34	197	1.27

The underlined numbers are different from those assumed by Wald. We did not exclude the wives of ex-smokers.
(1) Hirayama standardized by age of women only (from Table 2, Hirayama 1984)
(2) Hirayama with age selection bias removed (Überla and Ahlborn, 1987)

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Results

Meta-Analyses for All Possible Case-Control Study Combinations

In order to get a feeling for the consequences of random selection of studies, we first considered all possible combinations of case-control studies. With 10 case-control studies there are 1,023 possible study combinations or subsets for which a meta-analysis can be performed. We calculated them all. The results can be summarized as follows:

34.5% of all possible meta-analyses – using the Yusuf technique – are technically significant at $p \leqq 0.05$. That means that a random selection of studies leads to a probability of 65.5% for a negative result of the meta-analysis.

The Trichopoulos study is involved in 330 of the 353 significant study combinations, that is in 93.5%. This study is the dominant study in the significant combinations. Without the Trichopoulos study only 23 out of the 511 then possible study combinations are "significant", that is 4.5%. One has a probability of 95.5% for a negative result selecting a subset of studies for a meta-analysis randomly.

The Trichopoulos study was judged as methodologically unacceptable. It is a textbook example of how a case-control study should not be performed [29]. If it were included, however, the impact of this study on the results would prove to be heavy.

Table 3. Results of meta-analyses I

Author		Cohort only	Case-control quality +	Case-control quality −	Cohort plus CC quality +	All
Hirayama*		×			×	×
Garfinkel		×			×	×
Chan			×		×	×
Correa				×		×
Trichopoulos				×		×
Buffler			×		×	×
Kabath			×		×	×
Garfinkel			×		×	×
Akiba				×		×
Lee				×		×
Koo			×		×	×
Pershagen			×		×	×
Fisher:	p	0.017	0.604	0.007	0.137	0.009
Yusuf:	$\widehat{RR}$	1.271	1.074	1.652	1.178	1.260
	IL95	1.025	0.848	1.201	1.005	1.093
	IU95	1.575	1.361	2.272	1.381	1.453
	p**	0.014	0.277	0.001	0.022	0.001

* Hirayama standardized by age of women only, RR = 1.45 as calculated from Table 2, Hirayama, 1984

** one-tailed

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Table 4. Results of meta-analyses II

Author		Cohort only	Cohort plus CC quality +	All without Trichopoulos	All
Hirayama adjusted*		×	×	×	×
Garfinkel		×	×	×	×
Chan			×	×	×
Correa			–	×	×
Trichopoulos			–	–	×
Buffler			×	×	×
Kabath			×	×	×
Garfinkel			×	×	×
Akiba			–	×	×
Lee			–	×	×
Koo			×	×	×
Pershagen			×	×	×
Fisher:	p	0.105	0.336	0.158	0.028
Yusuf:	$\widehat{RR}$	1.013	1.035	1.076	1.118
	IL 95	0.848	0.941	0.941	1.273
	IU 95	1.210	1.193	1.230	1.299
	p**	0.443	0.317	0.142	0.046

* With age selection bias removed. RR = 0.902 (Überla and Ahlborn 1987)
** one-tailed

Meta-Analyses for Selected Study Groups

Meta-analyses for various combinations of cohort and case-control studies were calculated. The results are given in Table 3. For the Hirayama study a relative risk of 1.45 for the exposed versus non-exposed persons is used in all these combinations as one of the starting points. The results show that the probability using the Fisher method is always higher than the probability using the procedure as applied by Yusuf [32] or Wald [31]. This had to be expected. The other methods – Mantel-Haenzsel or for the cohort studies risk ratios – do not differ much from the Yusuf method. All the study combinations on Table 3 are significant with the exception of the reasonable quality case-control studies. These six studies have a common risk estimate of 1.07, being not statistically different from unity.

The meta-analyses for these study combinations were repeated using a relative risk of 0.90 for the Hirayama study as was calculated by Überla and Ahlborn [30]. The pooled risk estimates are very close to unity and are not statistically significant (Table 4). When one includes the Trichopoulos study, the pooled estimate for the relative risk is 1.118, approaching but not reaching statistical significance.

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Discussion

To summarize, the expected overall risk of dying of lung cancer for non-smoking women married to smoking men is:

- 1.074 out of six case-control studies of reasonable quality,
- 1.013 out of two prospective studies, using the Hirayama study with the age selection bias removed as shown by Überla and Ahlborn,
- 1.035 out of two prospective studies and six case-control studies of reasonable quality,
- 1.076 out of eleven studies, with the Trichopoulos study excluded, and
- 1.118 out of all twelve studies including the Trichopoulos study.

These risk estimates are not statistically different from unity.

Thus, the overall result of various meta-analyses can be summarized as follows: Meta-analysis of 12 relevant studies (using women only and adjusting the relative risk of Hirayama for age selection bias) gives an overall estimate of relative risk of dying of lung cancer for non-smoking women married to smoking men of $\widehat{RR} = 1.076$ (Trichopoulos excluded) or $\widehat{RR} = 1.118$ (Trichopoulos included). These risk increases of about 8% or 12% are not significantly different from unity.

Our results differ widely from the results given by Wald [31]. The main reasons are different relative risk estimates for the individual studies. The papers by Hirayama and Trichopoulos were the first studies to be published on this issue. All later studies give less indicative results. Whether wives of ex-smokers should be included or not, whether the Hirayama study has to be adjusted for age selection bias and whether the Trichopoulos study is methodologically as stringent as a case-control study should be is open for discussion and will be answered differently by individual scientists. We have shown a variety of possible outcomes of meta-analyses and demonstrated the sensitivity of the results with varying assumptions.

The whole question of meta-analyses comes down to the question of the quality of the individual study. As long as there are no better studies available, meta-analyses cannot and do not add much new evidence to the question whether passive smoking is related to lung cancer.

References

1. Akiba S, Kato H, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Res 46:4894–4807
2. Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. In: Grundmann E (ed) Cancer campaigne, vol 6. Cancer epidemiology. Gustav Fischer, Stuttgart, pp 199–202
3. Correa P, Pickle LW, Trontham E, Lin Y, Haenszel W (1983) Passive smoking and lung cancer. Lancet 2:595–597
4. Correa P, Pichler LW, Trontham E, Dalager E, Haenszel W (1984) The causes of lung cancer in Louisiana. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Chemie, Weinheim, pp 73–82
5. Dalager NA, Pickle LW, Mason ThI, et al (1986) The relation of passive smoking to lung cancer. Cancer Res 46:4808–4811
6. DerSimonian R, Laird N (1986) Meta-Analysis in Clinical Trials. Controlled Clinical Trials 7:177–188
7. Garfinkel L (1984) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J Natl Canc Inst 66:1061–1066

2023381628

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8. Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: a case control study. J Natl Canc Inst 75:463–469
9. Gillis CR, Hole DJ, Hawthorne VM, Boyle P (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Respir Dis (Suppl) 133:121–126
10. Grahame R (1978) Comparison of different trials. Rheumatol Rehabil (Suppl) 135–139
11. Hirayama T (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 282:183–185
12. Hirayama T (1983) Passive smoking and lung cancer. Consistency of association. Lancet 1:1425–1426
13. Hirayama T (1984) Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Chemie, Weinheim, pp 175–195
14. Hirayama T (1984) Cancer mortality in non-smoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 13:680–890
15. Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221
16. Knoth A, Bohn H, Schmidt F (1983) Passivrauchen als Lungenkrebsursache bei Nichtrauche-rinnen. Med Klin 78:66–69
17. Koo LC, Ho JHC, Saw D, Path C (1983) Active and passive smoking among female lung cancer patients and control in Hong Kong. J Exp Clin Cancer Res 4:367–375
18. Koo LC, Ho JHC, Saw D, Path C (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J Exp Clin Cancer Res 3:277–283
19. Koo LC, Ho JHC, Lee N (1985) An analysis of some risk factors for lung cancer in Hong Kong. Int J Cancer 35:149–155
20. Lee PN (1984) Lung cancer incidence and type of cigarette smoked. In: Mizell M, Correa P (eds) Lung cancer: Causes and prevention. Chemie International, Deerfield Beach, pp 373–384
21. Lee PN, Chamberlain J, Alderson HR (1986) Relationship of passive smoking to risk of lung cancer and other smoking diseases. Br J Cancer 54:97–105
22. Miller GH (1984) Cancer, passive smoking and nonemployed and employed wives. West J Med 140:632–635
23. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers ThC (1987) Meta-analyses of randomized controlled trials. N Engl J Med 316:450–455
24. Sandler DP, Everson RB, Wilcox AJ (1984) Passive smoking in adulthood and cancer risk. Am J Epid 121:37–48
25. Sandler DP, Wilcox AJ, Everson RB (1985) Cumulative effects of lifetime passive smoking on cancer risks. Lancet 1:312–315
26. Sandler DP, Everson RB, Wilcox AJ, Browder JP (1985) Cancer risk in adulthood from early life exposure to parents smoking. Am J Publ Health 75:487–492
27. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1–4
28. Trichopoulos D, Kalandidi A, Sparros L (1983) Lung cancer and passive smoking: conclusion of Greek study. Lancet 2:677–678
29. Überla K (1987) Lung cancer from passive smoking: hypothesis or convincing evidence? Int Arch Occup Environ Health 59:421–437
30. Überla K, Ahlborn U (1987) Passive smoking and lung cancer: a reanalysis of Hirayama's data. International Conference on Indoor Air Quality. Tokyo
31. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS (1986) Does breathing other people's tobacco smoke cause lung cancer? Br Med J 293:1217–1222
32. Yusuf S, Peto R, Lewis J, Collins R, Sleight P (1985) Beta blockade during and after myocardial infarction: an overview of the randomized trials. Progress in Cardiovascular Diseases Vol XXVII 5:338

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Review article

Lung cancer from passive smoking: hypothesis or convincing evidence?

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Summary. The epidemiological literature on passive smoking and lung cancer is reviewed and the well-known criteria for establishing a causal relationship are applied in order to determine what level of causal evidence currently exists. Three cohort studies and 12 case control studies are analysed. Of the prospective cohort studies, one contributes very little to our knowledge, one shows no risk increase and one results in a moderate risk increase of 1.74 for women married to heavy smokers. The last is the only study which has to be taken seriously, even when other considerations show that its results might be caused by chance, bias or confounding. None of the six case control studies yielding a positive relationship was conducted according to the state of art of epidemiological research, giving reasonable and sound evidence which cannot be explained by chance, bias, confounding or misclassification. Two studies contribute nothing to the evidence. None of the four case control studies yielding no risk change or a risk decrease can exclude the possibility that a causal relation exists. The epidemiological and toxicological evidence is discussed in the light of recent findings. The volume of accumulated data is conflicting and inconclusive. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk. Applying the criteria proposed by IARC there is a state of inadequate evidence. The available studies, while showing some evidence of association, do not exclude chance, bias or confounding. They provide, however, a serious hypothesis. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man.

Key words: Passive smoking – Lung cancer – Causal connection

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Introduction

Active smoking is the most important, avoidable health hazard in industrialized countries. If passive smoking causes lung cancer, this would be a very strong argument against active smoking. It could be the decisive argument for reducing active smoking considerably. Science should determine whether this hypothesis is true or not. If it is to do so, one must seek to state the facts and to separate these from mere speculation.

There are eight well established criteria which should be fulfilled if a causal connection in epidemiology is to be inferred:

- *Consistency* of the association in various studies. The results should be reproducible in similar circumstances.
- *Strength and intensity* of the association. Risk ratios of 5, 10 or greater are more likely to indicate a causal relationship than a risk ratio of around 2.
- *Specificity* of the association. The exposure, the effect and the way in which the exposure works should be specific. Therefore exposure and effects should be measured with sufficient validity and specificity.
- There should be a *dose-response relationship*.
- *Exclusion of bias and confounding factors.*
- There should be *statistical significance.*
- *Impact of intervention*, i.e. there should be studies showing a decrease of the effect when the exposition has been diminished.
- There should be *biological plausibility.*

Taking these criteria into consideration, the IARC has proposed four different levels of evidence [22] when evaluating the existence of a causal relationship regarding carcinogenicity in humans:

(1) Sufficient evidence of carcinogenicity: There is a causal relationship between the exposure and human cancer.
(2) Limited evidence of carcinogenicity: A causal interpretation is credible, however, alternative explanations (such as chance, bias, confounding) cannot adequately be excluded.
(3) Inadequate evidence: There are few pertinent data or the available studies, while showing evidence of association, do not exclude chance, bias or confounding.
(4) No evidence: Several adequate studies are available which do not show evidence of carcinogenicity.

In this article the available literature is examined in light of the criteria required to infer a causal connection and thus to determine what IARC level of causal evidence currently exists.

Cohort studies

Adequate and well conducted cohort studies can provide sound, empirical evidence on a causal relationship between exposure and event. To date, three cohort studies on passive smoking (from Hirayama, Garfinkel and Gillis et al.) have been published.

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Hirayama

Evidence from this study has been published in four reports [18, 19, 20, 21]. In addition there are several critical comments [4, 24, 32, 33, 34, 37, 38, 47, 48, 49, 54, 60]. Married, nonsmoking women aged 40 and above (n = 91540) from a cohort of 265118 adults in 29 health center districts in Japan were followed for 15 years. Altogether, 200 women died of lung cancer. Standardized mortality rates for lung cancer were calculated according to the smoking habits of the husbands. The point estimate of the rate ratio was 1.74 or 1.79 when comparing women of nonsmoking husbands to women whose husbands smoked more than 20 cigarettes per day. There was a dose-response relationship which was also significant. Standardization using the age of women and the occupation of husbands was performed. In nonsmoking men with smoking wives, seven lung cancer deaths occurred, resulting also in a relative risk of around 2.

In evaluating the results of this study the following points must be taken in consideration:

(1) The study was designed to screen for a wide variety of possible risk factors on life events and not to test the hypothesis that passive smoking causes lung cancer. It therefore cannot prove this hypothesis, but rather can only generate it. The hypothesis that passive smoking causes lung cancer is one of several secondary hypotheses which can be extracted from this material.

(2) The reported cohort is not representative of the population of Japan. The age distribution of females over 40 in Japan in 1965 was different from the age distribution in the cohort [44]. Of 265118 adults (122261 men and 142857 women) only 91540 nonsmoking married women, whose husbands smoking habits were known, were included in the study. 51317 women (35.9%) were not used, partly because the smoking habits of the husbands were not known and the corresponding 103 nonsmoking lung cancer cases were not entered in the study. Even when most of them were not married, some selection mechanism was at work. The precise effect of this selection, for instance, regarding occupation of wives, is unpublished and unknown.

(3) The indicator, by which the exposure to passive smoking was estimated, was neither specific nor was its reliability or validity assessed [24]. The state for a woman "being a nonsmoker and being married to a man who smokes a certain number of cigarettes" was registered once in 1965. The duration of this status is unknown and was not accounted for: A woman living with a smoker in 1965 for a year and then dying of lung cancer was treated as married to a smoker in the same way as a woman being a passive smoker for 30 years. A woman, who began smoking a year after the start of the study and who died of lung cancer, was treated as a nonsmoker. The exposure to sidestream smoke in the working place for women – approximately 45% for men and 25% for women of the total exposure in Germany [40] – is not contained in the indicator. Being married to a man who smokes might mean a lot of other risks influencing the cause of death, for instance risks from food, environment, social conditions, living in cities or in villages, size of living space at home, or occupation of the women. The selection of partners will most certainly introduce some other risk factors which have not been

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accounted for. It has been shown that being married to a man who smokes is consistent with a wide variety of exposure to sidestream smoke [11, 39, 59]. One study [11] shows, that 40 to 50% of persons with nonsmoking spouses reported some passive exposure and conversely 30 to 35% who were married to smokers reported no exposure. The concordance on directly and indirectly reported smoking habits of the spouse was 85% in another study [36]. Being married to a man who smokes is not a valid and accurate indicator of the extent to which one is exposed to passive smoking and is by no means specific.

(4) The event – dying from lung cancer – was not assessed in a way which corresponds to the state of the art. It is well known that the causes of death on death certificates disagree to a certain extent with the real cause of death. It is safe to assume that at least 10% have died from causes other than those specified on the death certificate. In one study [13], the cause of death on death certificates was not confirmed by the treating physician in 16.7% of the lung cancer cases. An autopsy was available from only 23 (11.5%) of the 200 cases. However, the histological type of lung cancer is decisive in establishing a causal connection. Women frequently have adenocarcinomas, a histological diagnosis that is not believed to be connected to smoking as strongly as squamous or small cell carcinoma. Neither the exposure nor the event were assessed or monitored in a way approaching the standards which are applied in other fields of risk evaluation, for instance in studies on adverse drug reactions.

(5) Various confounding factors were not adequately considered in this study; for instance, exposure to other substances in the working place, (dust, fumes or vapours), overall air pollution, exposure to indoor pollution, such as kerosene stoves, genetic condition, food, type of medical care and others.

(6) Bias in registering the fact that a woman was a nonsmoker, was neither controlled for nor excluded. Some women who were active smokers might have declared themselves nonsmokers in a society where smoking women were not well accepted and who made up an absolute minority. Such women developing lung cancer will then be included as cases.

(7) The percentage of possible misclassifications and its likely effect on the results have not been examined. With a certain percentage of misclassifications in the category "nonsmoking women" among the lung cancer cases, the statistical differences will disappear. Recent studies [26, 35] have shown that misclassification can easily explain the association between lung cancer and passive smoking in case control studies.

(8) Almost nothing was reported on the 200 cases. There are no case reports available, from which individual histories can be judged or at least partly evaluated regarding other relevant factors. This is standard in other areas, e.g. the evaluation of rare adverse side effects from drugs. The core of evidence we have on the cases is that, during 1965, 200 women in Japan told an interviewer on a single occasion that they were, at that time, nonsmokers, married to a smoker and their death certificate subsequently contained

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the (perhaps erroneous) diagnosis lung cancer. This information is not very convincing to a scientist.

(9) The trend in lung cancer rates in Japan between 1950 and 1979 was over nine-fold in men and over six-fold in women [31]. This risk increase cannot be explained by passive smoking. Comparing the total population to that of nonsmokers from Hirayama's own data, this ratio is only four-fold in men and just under two-fold in women. This indicates that there might be some other important cause of lung cancer which was not studied.

(10) Some statistical arguments have to be kept in mind: Nobody knows how many tests have been applied to this material. Adjustments for multiple tests, however, would considerably reduce significance levels. Statistical tests with huge numbers in the denominator are not as convincing as the accompanying small type I error indicates. The larger the number and the smaller the incidence, the more important are bias and confounding. For very small incidences, the theoretical models are not very appropriate. Diamond and Forrester [10], using a Bayesian approach, have shown how small the posterior probability for Hirayama's hypothesis could be. Using their analysis, Hirayama's results could well be consistent with the null hypothesis. The statistical significance of Hirayama's risk ratios could be a matter of chance or an artifact induced by some of the many problems occurring in such a large study.

Considering all these arguments, the study at best suggests the hypothesis of a causal association. Still, the null hypothesis might also be true. Even when a dose-response relationship seems to exist in this study, chance, bias or confounding factors could as adequately explain the results as does the hypothesis that passive smoking causes lung cancer.

Garfinkel

This re-analysis [13] uses data from the ACS-study [12] and from the Dorn study [57] in the USA. Nonsmoking women (n = 176, 739) married to men with known smoking habits were included. The period from 1955–1972 was covered. The relative risk adjusted for several factors was 1.04 when women married to nonsmokers were compared to women married to husbands smoking more than 20 cigarettes per day. There was no statistical significance and no dose-response relationship. The authors argue that if passive smoking is of practical importance, then there should be an increase in death rates due to lung cancer among nonsmokers. This could not be found.

The sample size and the level of details of this study are comparable to Hirayama's material. Some information, for instance on histology, is more specific. There is, however, no indication of a statistical connection between passive smoking and lung cancer. The paper failed to reproduce the Hirayama results and did not add evidence to this hypothesis. If there is a relevant increase in lung cancer risk from passive smoking, it should also have shown up in Garfinkel's study. The Garfinkel study does not of course disprove the Hirayama hypothesis.

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Gillis et al.

This study was published in 1984 [15] and presents only very few cases (6 men and 8 women) with lung cancer among nonsmokers. It does not show any trend or statistical significance because of these small numbers. This study contributes very little to the empirical evidence in either direction.

Summarizing the evidence from cohort studies, the conclusion is that only the Hirayama study, which has severe drawbacks, provides any empirical evidence in favour of the hypothesis that passive smoking may cause lung cancer in nonsmokers.

Case-control studies

In assessing the relative risk of rare events, case control studies can provide valuable information by estimating odds ratios. Such studies cannot prove a causal connection. They can, however, give sound empirical evidence, provided several studies have consistently similar results, the effect and the event are determined with some validity, the odds ratios are large and bias can be adequately excluded. Twelve case-control studies have been published so far on the relationship between passive smoking and lung cancer.

Trichopoulos et al.

In this study [55, 56], 77 nonsmoking women with lung cancer and 225 nonsmoking women with other diseases were compared with regard to the smoking habits of their husbands. The authors calculated an odds ratio of 2.4 and 3.4 when comparing women married to nonsmokers with women married to men who smoke less than one pack of cigarettes per day and more than one pack per day respectively. The linear trend of these ratios is significant. The authors were aware of some of the limitations of this study and concluded that further investigations were warranted.

The Trichopoulos study is a textbook example for some of the errors which must be avoided if a case-control study is to be valid:

- The cases are from three cancer hospitals, the controls from a hospital for orthopedic disorders. A systematic bias is therefore likely.
- An interviewer bias must be expected: the same medical doctor selected the controls and interviewed them. He was fully aware of the goal of the study.
- A bias in recalling the passive smoking history is likely in patients. At least some of the cases knew their diagnosis, whereas the controls were not aware of a life-threatening disease.
- Patients with adenocarcinoma and with alveolar carcinoma were excluded, so that there was a selection among the lung cancer cases. This makes it a study of a subset of lung cancer more associated with active smoking.
- The histological type of lung cancer is not available in 35% of the cases.
- In assessing the exposure, there is no specificity and no validity. Misclassification might have occurred [26, 35]. Being married to a cigarette smoker

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may not be a valid indicator of exposure to passive smoking and could indicate various other risks.
- Confounding factors, such as exposure at the work place, food, etc. were not considered.
- The calculated odds ratios are incorrect, they should be 1.95 and 2.54 [16].
- The risk of active smoking is on the same size order as that of passive smoking, a result that is biologically implausible.

The total number of cases is small. The statistically "significant" results of this study might well be artifacts from chance, bias or confounding. The study provides no valid evidence for a causal connection of passive smoking and lung cancer.

Correa et al.

Lung cancer patients ($n = 1338$) from a large number of hospitals in Louisiana were compared to 1393 controls from the same hospitals with regard to the smoking habits of spouses and parents [7, 8]. Eight male nonsmokers (from 1036) and 22 women nonsmokers (from 302) could be used for calculating odds ratios with regard to passive smoking.

The exposure was estimated in total lifetime pack-years by interviewing patients or their next of kin. Women married to smokers with more than 40 pack-years had an odds ratio of 3.52, which was significant ($P \leq 0.05$). Various other odds ratios were calculated but were within chance limits. The authors concluded that the similarity of their findings with those of Trichopoulos strengthened the suspicion that passive smoking may contribute to lung cancer. The study also revealed a relative risk of 1.66 for patients whose mothers smoked and of 1.04 if the father was a smoker. The relative risk for patients whose mother smoked decreased to 1.36 when one takes into account the active smoking of the subject. The effect of maternal smoking is only significant in males. How maternal smoking causes lung cancer in males, but not in females, can only be a matter of speculation according to the authors.

The numbers of nonsmoking cases are small. Misclassification could be a sufficient explanation for the association. In view of the many calculated odds ratios, one single ratio reaching $P \leq 0.05$ is not surprising. There might be a selection bias. 76% of the cases and 89% of the controls were interviewed by professional interviewers. It was not mentioned which percentage of the patients themselves and which percentage of the next of kin gave the information. This might be different in cases and controls. The inconsistencies in this publication can most easily be explained by the large number of odds ratios calculated from very few nonsmoking cases, by possible bias, by chance, or by confounding factors. The study does not provide convincing evidence for a causal relation between passive smoking and lung cancer.

Sandler et al.

The authors published three reports from the same data base [50, 51, 52], covering in the first paper the effect of smoking of the spouse, in the second

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paper the combined effect of father, mother and spouse, and in the third paper only the childhood exposure. Several critical comments have been published [5, 17]. Cancer cases from all sites (n = 518) were compared to 518 controls in the first paper, and an odds ratio of 1.6 for all cancer sites and one of 1.6 for lung cancer was reported.

These results are not very meaningful for a variety of reasons. Controls were selected by cases in 60%. The cases answered questions on smoking, knowing that they had cancer and that there is a relation between smoking and cancer. They proposed friends without cancer to answer questions on smoking, thereby possibly selecting friends with less exposure to smoke. The level of education differs significantly between cases and controls together with other confounding variables connected with education. The reporting was not comparable between cases and controls: the number of missing values on marital status and occupation are different and the same might have been the case in reporting on passive smoking. The results are not presented by age and sex of the nonsmokers, so that details of the calculations cannot be verified. Combining all types of cancer with different etiology and epidemiology does not make biological sense. The crude odds ratio for smoking is much smaller than the one for passive smoking, which is biologically implausible. The authors claim that passive smoking is related to a number of cancers not related to active smoking, which is not plausible, because active smokers are more exposed to sidestream smoke than nonsmokers. There was no clearcut dose-response relationship. Exposure outside the home was disregarded. Misclassification could explain part or all of the results. The evidence for lung cancer is especially weak: there were only 22 cases reported, 20 of them smokers, so that the whole evidence on passive smoking and lung cancer in this study is based on two nonsmoking lung cancer cases.

In the second and third papers, there is no further serious evidence on lung cancer caused by passive smoking. A large number of odds ratios and error probabilities is calculated, based essentially on the same two nonsmoking cases as in the first paper. Adjusting for multiple factors can add nothing to the evidence in such a case. There are at best hypotheses generated, most of which will not be reproducible in further studies.

Chan and Fung

In this paper [6], 84 female nonsmoking lung cancer patients were compared to 139 controls regarding the smoking habits of spouses. The authors gave the numbers, but did not calculate the odds ratio, which is 0.75 and within chance limits. This study – giving the histological type of tumor and some information on cooking habits – does not support the hypothesis that passive smoking causes lung cancer.

Koo et al.

Koo et al. have presented three papers on the subject [28, 29, 30], giving an analysis of risk factors in 1781 lung cancer cases from Hongkong in the first. Since it is not evident from the second and third papers whether they refer at

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least partially to the same cases, only the second paper with 200 cases and 200 controls is considered here. The third paper with 120 cases and 120 controls had very similar results.

Two hundred female lung cancer cases were compared with 200 female controls regarding the exposure to passive smoking. Eighty-eight cases and 137 controls had never smoked (66 and 97 with passive smoke exposure, odds ratio 1.24) and 112 cases and 63 controls had smoked. The histological diagnosis is provided for all cases. A very detailed interview of all cases and controls was conducted by trained interviewers. The information on the patients and controls is more detailed than in all other studies. The exposure to sidestream smoke at home and at work was included in the analysis and an attempt was made to quantify exposure. The calculated odds ratio is not significant. There was no dose-response relationship. The original 200 cases and controls were age-matched. However, these who had never smoked could have had another age distribution and no age standardisation was carried out. This study does not support the hypothesis that passive smoking causes lung cancer.

Kabat and Wynder

The authors [25] compared 134 nonsmokers out of 2668 lung cancer patients with 134 nonsmoking controls, which were age-, race- and hospital-matched. The groups were comparable regarding religion, proportion of foreign born, marital status, residence, alcohol consumption and Quetelets index. Male cases tended to have higher proportions of professionals and to be more highly educated than controls. No difference in occupation or occupational exposure was seen in men. The histological type of lung cancer in lifelong nonsmokers and in smokers was described for 882 men and 652 women. Information on passive smoking was available in 25 male cases and controls and in 53 female cases and controls. Spouses' current or past smoking habits were known in 36 cases and controls. There was no increase in risk comparing exposure at home or at work in women, and in men at home. Only in the subgroup of men with exposure at work was there a risk increase for the cases, the difference being just significant ($P \leq 0.05$). Such subgroup analyses are however misleading. Overall this study does not support the hypothesis that passive smoking causes lung cancer.

Miller

In this paper [43] information was gathered (telephone interviews with the next of kin) from 1838 cases out of 4130 deaths in Pennsylvania during 1975 and 1976. Nonsmoking women ($n = 537$), who were married and of whom there was information on the smoking habits of the husband, were analysed.

Odds ratios were calculated for various subgroups comparing all cancer deaths with all deaths by other causes regarding the smoking habit of the husband. The author concluded that the results of the study provide support for the hypothesis that long-term passive smoking leads to excess cancer deathrates in

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exposed nonsmokers. The data simply do not support such an hypothesis. In particular:

- 44% of the available deaths were omitted because of incomplete information.
- If the correct formulas are applied to the data and if age standardization is performed, the odds ratios are well within chance limits.
- Confounding factors and bias in reporting are not seriously considered.

This study, since it was not performed according to the state of the art, adds nothing to our knowledge.

Garfinkel et al.

In this case-control study [14] the authors compare 134 carefully selected nonsmoking women with lung cancer to 402 controls with cancer of the colon/rectum. The cases were selected from hospital records and special attention was given to a verified histological diagnosis. The exposure to passive smoking was assessed by a standard interview and a quantification of the exposure was attempted. The overall result was – considering the total exposure at home and at the working place – that there is no significant risk increase. The odds ratio was 1.28 for the exposure during the last five years and 1.12 for the last 25 years. There was no dose-response relationship regarding the overall exposure. Analysing various subgroups, there was one subgroup with a marginally significant risk increase: women married to men smoking more than 20 cigarettes per day at home (OR = 2.11, $P \leq 0.05$). There is no evidence of a passive smoking relationship where the data come from the woman or her husband. The odds ratios (OR) increased if the exposure history was not taken from the patient herself or from her spouse, but rather from other relatives or friends. A logistical regression analysis, adjusting for age, hospital, socio-economic status and year of diagnosis, arrived at approximately the same type I error rate.

This meagre result is weakened by the following considerations:

- A bias due to misclassification of active smoking might exist. The smoking habit was assessed in more than half of the cases not by themselves or by their husbands, but rather by their children or someone else. This was done several years after the diagnosis, in many cases several years after death, and the relevant information had to include the time 20 and more years before. Active smoking of some cases that long ago might not have been known to the person interviewed.
- There is no evidence of an association when the data on smoking habits came from the woman themselves or from their husbands; it only appeared when the daughter, son or another person supplied the information.
- A lot of odds ratios were calculated in subgroups, which were not independent. If one adjusted for multiple testing, none of the slightly significant numbers would remain significant. The analysis of subgroups using confidence intervals quite often leads to invalid results and in this study also the negative fluctuations around the chance level have to be considered.
- The study presents direct evidence that misclassification of the subject smoking habits can bias estimates of passive smoking upwards. A strong associa-

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tion is seen in the analysis of data based on hospital records and a much weaker association is seen after partially correcting for it.

— The high percentage of adenocarcinomas which are less typical of active smoking could explain the meagre result of this study.

The study does not provide evidence to support the hypothesis that passive smoking causes lung cancer.

Lee et al.

In the latter part of a large hospital case-control study [36] of 56 lifelong, nonsmoking lung cancer cases who were married once, 34 spouses were successfully interviewed on their cigarette consumption. A wide range of potential confounding factors was considered. The spouses of 80 matched controls, whose condition was not related to smoking, were interviewed in the same way. Various odds ratios were calculated. Passive smoking was not associated with any significant increase in risk of lung cancer amongst lifelong nonsmokers. The overall relative risk was 0.80 with an upper confidence limit of 1.50, which is less than some of the larger increases claimed in other studies. The authors discussed limitations of past studies and concluded that any risk increase by passive smoking is at most small and may not exist at all.

The number of cases in this study is small and the type II error is therefore large. The study does not contribute positive evidence to the hypothesis that passive smoking causes lung cancer, nor does it disprove it.

Akiba et al.

Lung cancer cases and controls from Hiroshima and Nagasaki atomic bomb survivors were compared in this study [1]. There were 113 nonsmoking lung cancer cases, 94 of them women. Various odds ratios were calculated. The authors reported an overall odds ratio of 1.5 for lung cancer among nonsmoking women whose husbands smoked, which was just not significant at conventional levels. The risk tended to increase with amount smoked by the husband and to decrease with cessation of exposure.

Most of the cases had died before the study was conducted. In only about 10% of the cases could the smoking habits of the husband and other information be obtained directly from the cases. Only 52% of the cases were verified by autopsy. There is some possibility of bias in this study left: a fact that led the authors to conclude that further studies were warranted where passive smoking exposure could be more fully quantified.

Dalager et al.

The authors [9] combined the cases from three case-control studies which had been published earlier [3, 7, 62]. Ninety-nine nonsmoking, histologically confirmed lung cancer cases were compared to 736 controls. The cooperation rate, the source of passive smoking data, the gender groups included, the racial

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groups included and the study design varied between Louisiana, Texas and New Jersey. The original studies had opposite outcomes, Louisiana showing a positive relationship, and Texas a negative one. Only the home exposure to passive smoking was considered. There was no increase in the risk of lung cancer controlling for gender, age and study area as confounders (OR = 0.84). Searching in subgroups, several analyses were performed leading to an odds ratio of 1.47 (only Louisiana and New Jersey, only smoking pattern of spouse), which was not significant. A dose-response relationship occurred only among females with increasing pack-years of exposure to spouse smoking, with an OR = 2.99 for females with more than 35 pack-years of exposure. Here studies were not combined, and only Correa's Louisiana data were reiterated. Considering histological types, the adjusted odds ratios were also not significant. The highest OR = 2.88 was found for squamous and small cell carcinoma.

Most of the calculated odds ratios do not approach significance levels. The same sources of bias are existent here as in the study from Correa. Subgroup analyses have no confirmatory value. There was no adjustment for multiple testing. Misclassification might be present. The study does show that the same type of bias could be present in all three case control studies. Especially in older females, whose husbands are heavy smokers, bias might be more important. Any effect seen was limited to one of the three states, was of marginal significance and of doubtful validity. This study, combining data from three sources and searching in subgroups, does not contribute convincing evidence for the hypothesis that passive smoking causes lung cancer.

Knoth et al.

This study [27] is not a case-control study in the strict sense. The authors found that from 39 female nonsmoking lung cancer cases, 24 (61.5%) were married to a smoking husband or were living together with a smoker. They compared this percentage with the percentage of smoking men 50 to 69 years of age in the population, which was, according to their sources, nearly three times smaller (22.4%). They felt that passive smoking was the most likely explanation. In comparing these two percentages, other explanations are at least equally likely.

The real percentage of female nonsmoking lung cancer cases married to smoking males might be smaller than the one calculated from the study group. The smoking habit was known only for approximately 35% of the original group, making selection bias and interview bias a distinct possibility. More answers can be expected from couples with a smoking husband. The duration of smoking and the time of exposure was not clearly specified, nonsmoking men who had been smokers were also included. The percentage of female lung cancer cases married to cigarette smokers is not a valid indicator of exposure.

On the other hand, the percentage to be expected in such a group was not estimated properly. Around 38.6% of the men were active smokers in the "microcensus" conducted by the Federal Office of Statistics in 1980. In this census the definition of smoking is different from the one used in the study group. The selected age of 50 to 69 years is not well matched to the age of men in the study group and 22.4% was the average percentage of both male and

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female smokers. 58% of all men and women in Germany are smokers at some time during their life [40] and of these 36.7% are smokers. The percentage of men who smoked sometime during their life is higher than 58% in the older age groups in men, most likely around two thirds of the population. It is therefore not unexpected that 61.5% of female lung cancer cases were married to such men.

Comparing two improperly estimated percentages is not an acceptable method for epidemiological reasoning. This study adds nothing to the evidence that passive smoking might cause lung cancer.

Epidemiological evidence

To date, there have been no animal studies published in which lung cancer is produced by applying sidestream smoke. Evidence on a causal relationship between passive smoking and lung cancer can therefore only be based on epidemiological studies in man.

Of the three prospective studies, only one [18, 20] shows a moderate risk increase of 1.74. This study by Hirayama cannot be regarded as really indicative, because it might be seriously flawed. It is, however, the only study which, since it does give some empirically sound evidence, should be taken seriously.

Of the 12 case-control studies, two [27, 43] contribute nothing to the evidence, six show a moderate risk increase [1, 8, 9, 14, 50, 56], but do not sufficiently exclude chance, bias and confounding, four studies [6, 25, 29, 36] show a moderate risk decrease or no risk change. The histological type of tumor is not adequately reported in most of the case-control studies, the exposure is not assessed with reasonable validity, and interviewer bias might be present in most of them.

The major trend of the evidence in the published studies is not clearly in favour of the hypothesis. There is no single study published so far according to the state of the art of epidemiological research which gives reasonable, sound evidence.

All studies with positive associations can just as well be explained by change, bias, confounding or misclassification. Such poorly conducted and inconclusive studies cannot be added or pooled to get convincing evidence, as has been attempted in serious efforts to evaluate the situation [16]. Science should disregard poor studies. False plus false does not equal true.

Going through the eight accepted criteria mentioned in the introduction, only two of them – dose-response relationship and statistical significance – are partly fulfilled if one treats the Hirayama study as conclusive. There is no consistency in the various studies in the sense that the same results are reproduced in similar circumstances. On the contrary the results vary widely. The relative risk increase is small and at best around 2. The exposure and the effect have not been measured with validity and specificity. Bias and confounding factors have not been carefully excluded. There are no intervention studies. The biological plausibility is not convincing. Overall a causal connection cannot be inferred. Applying the IARC levels of evidence, one comes to the conclusion: in-

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adequate evidence. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk [23].

Discussion

If passive smoking were an important causal factor for lung cancer, smoking pipes would be a much higher risk for lung cancer than it is. Nonsmoking barkeepers and stewards should have increased lung cancer incidence, which has not been shown. Lung cancer would be much more frequent among nonsmokers – only 5 to 10% of lung cancer cases are nonsmokers. There would also have to be an increase in the incidence of lung cancer in nonsmokers, but this incidence has been rather stable during the last decades [13, 61], as far as we know. There should be histological pre-stages in passive smokers as there are in smokers. This is also not known.

Recent studies [26, 35] have shown that misclassification alone can explain the results of the available case-control studies. Estimating the exposure to passive smoking by cotinine measurements in urine [2, 40, 41] without quality control, and in the way as it has been done in studies so far [42, 58], is not a valid and reliable indicator of exposure of individual cases. A recent evaluation of the evidence on passive smoking [46] could not consider these facts, which were presented at a symposium [45] in October 1986. Whether the presence of many animal carcinogens in sidestream smoke alone – contrasted by missing epidemiological evidence – is a reasonable argument for the assumption that passive smoking causes lung cancer in man, remains an open question.

The toxicological evidence as summarized in [16] is based on exposure data and one the existence of carcinogenic and mutagenic substances in sidestream smoke alone. It is well known that the yield (per cigarette) of several carcinogenic substances and tar is higher in sidestream smoke than in mainstream smoke. The differences are partly due to modern filter techniques. However, analytical measurements of carcinogenic substances in sidestream smoke vary 2 to 10 times, depending on the measuring techniques. The dilution in the air and the physical and chemical processes in the air one or more hours after pollution by sidestream smoke have only recently been investigated [53], showing a fast decay of toxic effects within a short time. To what extent the various carcinogenic substances in sidestream smoke dilute or decay, depending for instance on time length, should be further investigated. Whereas the absorption of nicotine and its pharmacokinetic and metabolism are relatively well known, this does not hold for a single carcinogenic substance contained in sidestream smoke. The amount of absorption of these substances – not the amount inhaled –, how they act on the lung tissue, the metabolic pathways in the body and the way in which they act in man, are not known.

What is known is that there are many carcinogenic substances in sidestream smoke in very small concentrations. The evaluation of this fact depends on the frame of reference. If there is really no threshold for carcinogenic substances – which is the paradigm to which some leading toxicologists presently adhere, but

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References

1. Akiba S, Kat
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2. Biber A, Sche
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3. Buffler PA, Pi
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4. Burch PRJ (19
5. Burch PRJ (19
6. Chan WC, Fur
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7. Correa P, Pick
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8. Correa P, Pick
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9. Dalager NA, I
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10. Diamond GA,
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11. Friedman GP,
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12. Garfinkel L (1
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which might not be valid for a variety of reasons – and if every risk increase, however small and unlikely it could be, should be avoided, the conclusion must be that passive smoking should be banned from toxicological evidence alone. The first "if" will be answered by toxicology during the next decade and the second "if" should be left to decisions of the society and its institutions and not to toxicologists alone.

We should do all we can to reduce active smoking. Using the argument that epidemiological studies show passive smoking causes lung cancer – if this is not true – might be an obstacle to this goal in the long run. Such a possibly wrong argument might have serious negative effects on the credibility of epidemiology, which should be neither servant of the spirit of the age nor maid of toxicology. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man.

Acknowledgements. I want to thank H. W. Letzel, and L. C. Johnson for reading the manuscript and for helpful comments.

References

1. Akiba S, Kato H, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Res 46:4894–4807
2. Biber A, Scherer G, Hoepfner I, Adlkofer F, Heller WD, Haddow JE, Knight GJ (1987) Determination of nicotine and cotinine in human serum and urine: an interlaboratory study. Toxicol Lett 35:45–52
3. Buffler PA, Pickle LW, Mason TI, Coutant L (1984) The causes of lung cancer in Texas. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Verlag Chemie, Weinheim, pp 83–99
4. Burch PRJ (1981) Br Med J 282:1393
5. Burch PRJ (1985) Lifetime passive smoking and cancer risk. Lancet 1:866
6. Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. In: Grundmann E (eds) Cancer campaigne, vol 6, cancer epidemiology. Gustav Fischer, Stuttgart, pp 199–202
7. Correa P, Pickle LW, Fontham E, Lin Y, Haenzel W (1983) Passive smoking and lung cancer. Lancet 2:595–597
8. Correa P, Pickle LW, Fontham E, Dalager E, Haenzel W (1984) The causes of lung cancer in Louisiana. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Verlag Chemie, Weinheim, pp 73–82
9. Dalager NA, Pickle LW, Mason ThI, Correa P, Fontham E, Stenhagen A, Buffler PA, Ziegler G, Fraumeni JF (1986) The relation of passive smoking to lung cancer. Cancer Res 46:4808–4811
10. Diamond GA, Forrester JS (1983) Clinical trials and statistical verdicts: Probable grounds for appeal. Ann Int Med 98:385–394
11. Friedman GP, Petitti DB, Bawol RD (1983) Prevalence and correlates of passive smoking. Am J Publ Health 73:401–405
12. Garfinkel L (1980) Cancer mortality in nonsmokers: Prospective study by the American Cancer Society. J Natl Canc Inst (USA) 65:1169–1173
13. Garfinkel L (1984) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J Natl Canc Inst (USA) 66:1061–1066
14. Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: a case control study. J Natl Canc Inst (USA) 75:463–469

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

15. Gillis ChR, Hole DJ, Hawthorne VM, Boyle P (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Resp Dis [Suppl 65] 133:121–126
16. Henschler O (ed) (1985) Passivrauchen am Arbeitsplatz. Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe der DFG Weinheim; Deerfield Beach FL VCH
17. Higgins J (1985) Lifetime passive smoking and cancer risk. Lancet 1:867
18. Hirayama T (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 282:183–185
19. Hirayama T (1983) Passive smoking and lung cancer. Consistency of association. Lancet 1:1425–1426
20. Hirayama T (1984) Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizelli M, Correa P (eds) Lung cancer: causes and prevention. Verlag Chemie, Weinheim, pp 175–195
21. Hirayama T (1984) Cancer mortality in non-smoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 13:680–890
22. IARC Working Group (1985) IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans, vol 36. Lyon, pp 18/19
23. IARC Working Group (1985) IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans, vol 39: tobacco smoking. Lyon, pp 312–314
24. Johnson LC, Letzel HW (1984) Measuring passive smoking: methods, problems and perspectives. Prev Med 13:705–716
25. Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221
26. Kilpatrick Jr JS (1987) Exposure misclassification as an interpretation of some case control studies of ETS and lung cancer in nonsmoking women. Toxicol Lett 35:163–168
27. Knoth A, Bohn H, Schmidt F (1983) Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen. Med Klin 78:66–69
28. Koo LC, Ho JHC, Saw D, Path C (1983) Active and passive smoking among female lung cancer patients and controls in Hong Kong. J Exp Clin Cancer Res 4:367–375
29. Koo LC, Ho JHC, Saw D, Path C (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J Exp Clin Cancer Res 3:277–283
30. Koo LC, Ho JHC, Lee N (1985) An analysis of some risk factors for lung cancer in Hong Kong. Int J Cancer 35:149–155
31. Kurihara M, Aoki K, Tominaga S (eds) (1984) Cancer mortality statistics in the world. Nagoya
32. Lee PN (1981) Br Med J 283:1465
33. Lee PN (1984) Passive smoking. In: Cumming G, Bonsignore G (eds) Smoking and the lung. Plenum Publ Corp, New York
34. Lee PN (1985) Lifetime passive smoking and cancer risk. Lancet 1:1444
35. Lee PN (1987) Lung cancer and passive smoking: association and artefact due to misclassification of smoking habits? Toxicol Lett 35:157–162
36. Lee PN, Chamberlain J, Alderson HR (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 54:97–105
37. Lehnert G (1981) Krank durch Passivrauchen? Münch Med Wochenschr 123:1485–1488
38. Lehnert G, Garfinkel L, Hirayama T, Schmähl D, Überla K, Wynder EL, Lee P (1984) Round table discussion. Prev Med 13:730–746
39. Letzel HW, Johnson LC (1984) The extent of passive smoking in the FRG. Prev Med 13:717–729
40. Letzel HW (1986) Vortrag vor der AG Krebsgefährdung und Rauchen des BMJFG, 23.1.86, Bonn
41. Letzel HW, Fischer-Brandis A, Johnson LC, Überla K, Biber A (1987) Measuring problems in estimating the exposure to passive smoking using the excretion of cotinine in humans. Toxicol Lett 35:35–44
42. Matsukura S, Taminato T, Kitano N, Semo Y, Hamada H, Uchikashi M, Nagima H, Hirata Y (1984) Effect of environmental tobacco smoke on urinary cotinine excretion in nonsmokers. Evidence for passive smoking. N Engl J Med 311:828–832

43. Miller GH (1
J Med 140:6
44. Ministry of F
45. Norpoth K,
posium on pa
46. Peto J, Doll
47. Rose GA (19
48. Rutsch M (1
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49. Rylander R,
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50. Sandler DP,
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51. Sandler DP,
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52. Sandler DP,
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53. Sonnenfeld G
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54. Schievelbein
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55. Trichopoulos
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56. Trichopoulos
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57. Vaken HA (1
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58. Wald NJ, Bor
as a marker o
59. Weiß ST (198
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60. Wynder EL,
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61. Wynder EL (1
62. Ziegler RG, M
Altman R, Fr
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43. Miller GH (1984) Cancer, passive smoking and nonemployed and employed wives. West J Med 140:632–635
44. Ministry of Foreign Affairs of Japan (1967) Statistical survey of the economy of Japan: 4
45. Norpoth K, Mohtashamipur E (ed) (1987) International experimental toxicology symposium on passive smoking. Essen 1986. Toxicol Lett 35:1–168
46. Peto J, Doll R (1986) Guest editorial: Passive smoking. Br J Cancer 54:381–383
47. Rose GA (1982) Passivrauchen. Dtsch Ärztebl 79:30–32
48. Rutsch M (1981) Mangelhafte statistische Absicherung. Münch Med Wochenschr 123: 1484
49. Rylander R, Petersen Y, Snella MC (1984) ETS-Environmental tobacco smoke. Report from a workshop on effects and exposure levels. Eur J Resp Dis [Suppl 65] 133:129–130
50. Sandler DP, Everson RB, Wilcox AJ (1985) Passive smoking in adulthood and cancer risk. Am J Epid 121:37–48
51. Sandler DP, Wilcox AJ, Everson RB (1985) Cumulative effects of lifetime passive smoking on cancer risks. Lancet 1:312–315
52. Sandler DP, Everson RB, Wilcoxon AJ, Browder JP (1985) Cancer risk in adulthood from early life exposure to parents smoking. Am J Publ Health 75:487–492
53. Sonnenfeld G, Griffith RB (1987) The effect of smoke age and dilution on the cytotoxicity of sidestream (passive) smoke. Toxicol Lett 35:89–94
54. Schievelbein N (1981) Interview mit L. Garfinkel: Nicht vom eigentlichen Problem ablenken. Münch Med Wochenschr 123:1483
55. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1–4
56. Trichopoulos D, Kalandidi A, Sparros L (1983) Lung cancer and passive smoking: Conclusion of Greek study. Lancet 2:677–678
57. Vaken HA (1966) The Dorn study of smoking and mortality among US veterans: A report on 8–15 years observations. Natl Canc Inst Monog 19:1–125
58. Wald NJ, Boreham J, Bailey A, Ritchie C, Haddow JE, Knight G (1984) Urinary cotinine as a marker of breathing other people's tobacco smoke. Lancet 1:230–231
59. Weiß ST (1986) Editorial: Passive smoking and lung cancer. What is the risk? Am Rev Respir Dis 133:1–3
60. Wynder EL, Goodman NT (1983) Smoking and lung cancer: some unresolved issues. Epid Rev 5:177–207
61. Wynder EL (1986) Discussion on passive smoking, a risk on working place, Wiesbaden
62. Ziegler RG, Mason TI, Stenhagen A, Hoover R, Schoenberg JB, Gridley G, Virgo PW, Altman R, Fraumeni JF (1984) Dietary carotene and vitamin A and risk of lung cancer among white men in New Jersey. J Natl Cancer Inst (USA) 73:1429–1435

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The risk ratios for passive smoking can be surprisingly high (up to 2 or 3), as reported both by Correa et al and others.[8,9] These risk ratios would be more consistent with those found for active smoking, particularly among women, if the active smoker is at greater risk also from his or her own passive smoke, again through the absorption of radioactivity on the smoke particles passively inhaled; also the relatively higher toxicity of the sidestream smoke[10] might be important.[11] These and other aspects (eg, the urban-rural difference in lung cancer risk from smoking) are more thoroughly discussed elsewhere[12] in the context of indoor radon daughters. Finally, in view of the long latency periods observed among miners acquiring lung-cancer from radon daughter exposure,[13] one might suggest that the children of smoking mothers obtain an early exposure to increased levels of radon daughters at home and that smoking later in life promotes the development of lung cancer.

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HANS BERGMAN
OLAV AXELSON

LUNG CANCER AND PASSIVE SMOKING

SIR,—I was surprised to read, in Professor Trichopoulos and colleagues' letter (Sept 17, p 677), a German study of passive smoking and lung cancer described as having yielded "positive" results. The paper cited[1] contains only tentative conclusions based on poor data analysed by unacceptable methods.

I was also surprised that the findings from the Greek hospital study of passive smoking and lung cancer were almost identical to those reported two years ago[2] despite a substantial increase in the numbers of cases and controls. In the 1981 report the relative risks of lung cancer for non-smoking women were 1, 1·8, 2·4, and 3·4 according to whether their husbands did not smoke, were ex-smokers, or were current smokers of 1–20 or 21 or more cigarettes a day; the updated relative risks are 1, 1·9, 2·4, and 3·4, respectively.

In the 1981 paper the relative risks agreed exactly with the appropriate cross-product ratios calculated from the numbers of cases and controls in the relevant category for husbands' smoking. In the latest results, despite the method being apparently identical, there is a clear disagreement between the relative risks provided by Trichopoulos et al and those I calculate (see table).

RELATIVE RISK OF LUNG CANCER ACCORDING TO SMOKING HABITS OF HUSBAND

Group	Non-smokers	Ex-smokers	Cigarettes per day (current smokers)	
			1–20	21+
RR (quoted)	1·0	1·9	2·4	3·4
RR (calculated)	1·0	1·9	1·9	2·5

Relative risk = ratio of risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are non-smokers.

My calculations suggest that the latest data do not show as clear an association between a woman's lung cancer risk with her husband's smoking habits as the earlier data did. Indeed, relative risks calculated from the additional data are 1, 2·0, 1·8, and 1·8 and do not show the dose-response relation seen earlier. This doubt, added to doubts about the histological evidence and the use of cases and controls from different hospitals (limitations which Trichopoulos et al concede), prompts one to ask if the study really does add to the evidence implicating passive smoking as a factor in lung cancer.

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WOLF-DIETER HELLER

POTASSIUM CHLORIDE SUPPLEMENTS

SIR,—As your Round the World correspondent predicted,[1] the US Food and Drug Administration advisory committee meeting of March 2 on the controversy of wax-matrix versus microencapsulated potassium chloride preparations proved inconclusive. A few points about this controversy are worth noting.

The study by McMahon et al,[2] showing a favourable result for 'Micro-K' (A. H. Robins) in comparison with 'Slow-K' (Ciba-Geigy) was sponsored by Robins. The study by Patterson et al,[3] showing no difference between micro-K and slow-K, was sponsored by Ciba-Geigy. Both studies have been confirmed by other studies sponsored by the respective company.

Ciba-Geigy, while denying that slow-K is more ulcerogenic than micro-K, has bought from Alfred Benzon Ltd, Denmark, a licence for 'Kalinorm', a microencapsulated (pellet) preparation of KCl similar (or identical) to micro-K. It seems remarkable that Ciba-Geigy is planning to market this preparation when, according to Ciba-Geigy's US subsidiary, "Slow-K has an established clinical record unparalleled by any other solid K supplement".

It seems that, privately, Ciba-Geigy has concluded that kalinorm is as good as micro-K, and that it is better than slow-K, but they would presumably consider it scientifically incorrect to conclude that micro-K is better than slow-K.

Finally I would emphasise, as your RTW correspondent did, that doctors should "re-evaluate the decisive need for a potassium supplement and, if the indication is clear, prescribe it as a liquid". The findings of Patterson et al[3] clearly support this.

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OLLE HANSSON

***This letter has been shown to Dr Burley, whose reply follows.—ED. L.

SIR,—One of the main reasons why slow-release formulations of potassium were developed was the unacceptability of liquid potassium. Indeed, Patterson et al[3] reported that KCP elixir was poorly tolerated in their trial, giving rise to abdominal pain and heartburn in 9 of the 15 volunteers (60%). Dr Hansson omits to mention this. The issue is therefore whether the risk/benefit ratio of 'Slow-K' is acceptable. There are eighteen years of clinical experience with slow-K in the UK, during which over 4·5 million patient-years of treatment has been prescribed: with 'Micro-K' formulations there is almost no clinical experience. Less than 50 cases of significant alimentary side-effects have been reported with slow-K, and some of these were manifestly brought about by previous strictures or oesophageal obstruction due to cardiac enlargement. It would be hard to point to a comparable safety record with any other widely used drug. The fact that a company may be investigating or pursuing alternatives is an indication of interest and involvement in the area, and should not be interpreted as a loss of confidence in an existing product.

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DENIS BURLEY

8. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br Med J* 1981; 282: 183–85.
9. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer* 1981; 27: 1–4.
10. Surgeon General. The health consequences of smoking: Cancer. Washington, DC: US Dept of Health, Education and Welfare, 1982; DHHS (PHS) 82–50179.
11. Stock SL. Passive smoking and lung cancer. *Lancet* 1982; i: 1014–15.
12. Axelson O. Room for a role for radon in lung cancer causation. *Med Hypoth* (in press).
13. Axelson O, Sundell L. Mining, lung cancer and smoking. *Scand J Work Environ Health* 1978; 4: 46–52.
1. Knoth A, Bohn H, Schmidt F. Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen. *Med Klin Prax* 1983; 78: 54–59.
2. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer* 1981; 27: 1–4.
1. Anon. Potassium supplements and upper gastrointestinal tract. *Lancet* 1983; i: 466.
2. McMahon FG, Akdamar K, Ryan JR, Erian A. Upper gastrointestinal lesions after potassium chloride supplements: a controlled clinical trial. *Lancet* 1982; ii: 1059–61.
3. Patterson DJ, Weinstein GS, Jeffries GH. Endoscopic comparison of solid and liquid potassium chloride supplements. *Lancet* 1983; ii: 1077–78.

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CONFOUNDING FACTORS

Introduction

According to a 1990 publication by a Swedish scientist, Dr. Ragnar Rylander:

> Studies evaluating the hypothesis of a relationship between exposure to environmental tobacco smoke and lung cancer must take into account other environmental risk or protection factors and the possibility that exposure to environmental tobacco smoke may be confounded. This has not been done in the majority of such studies. Until this has been done, the claim of causality between environmental tobacco smoke and lung cancer remains uncertain. [Emphasis added.][1]

In epidemiologic studies, confounders are variables which can affect the outcome of interest, independently of the factor under investigation. Potential confounding factors in studies of ETS and lung cancer are numerous and varied.[2] It is difficult to control for all of them in the design of an epidemiologic study. Following are lists of some of the possible confounders encountered in epidemiologic studies of lung cancer incidence in nonsmokers, both those specifically considering ETS and those dealing with other factors.

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Heating and Cooking Fuels

- In developing countries, the use of certain fuels (kerosene, gas, coal, liquefied petroleum gas, straw, or wood) for heating and cooking contributes to elevated levels of indoor air pollution, which may contribute to disease incidence.[3]

- Following earlier, limited reports[4] on exposures to fumes from the use of various fuels, eight studies examining coal use in stoves and other indigenous heating devices in China have recently been published.[5-12] RRs as high as 14 have been reported,[8] although most RRs are in the 1.0 to 2.0 range.[11,12]

- Some fuels, namely, kerosene or coal and wood or straw, have been associated with a increased risk of lung cancer in Japanese women as well.[13,14]

Cooking Techniques

- The use of certain cooking oils and some cooking techniques (i.e, stir-frying and deep frying) which produce oil vapors have been associated with increased lung cancer risks in Chinese women.[11,15]

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Air Pollution

- In addition to indoor air pollution from heating and cooking fuels, as described above, outdoor air pollution has been associated with increased lung cancer incidence in at least one epidemiologic study in northeast China.[12]

Dietary Factors

- Increased lung cancer risk has been associated with the consumption of smoked, salted, cured, pickled, processed, or spicy foods among Oriental women.[18] Additionally, research suggests that wives whose husbands smoke may consume more processed and spicy foods and eat fewer fresh fruits and vegetables than do those whose husbands do not smoke.

- One study reported an elevated lung cancer risk among Oriental women associated with the consumption of green or black tea.[17]

- It has also been reported that nonsmokers married to smokers have lower intakes of dietary carotene, a substance associated with decreased cancer risks when consumed in sufficient amounts.[18] Recently, an abstract reported an correlation between serum carotene levels and socioeconomic status; this

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could be important if smoking and SES are also correlated, as has been suggested.

Occupation

- Some of the studies considering lung cancer in nonsmokers have also reported elevated relative risks associated with employment in certain fields or with occupational exposures to certain substances.[5,11-13]

Medical and Lifestyle Factors

- Personal health factors such as menstrual cycle length and previous history of respiratory disease (including tuberculosis, pneumonia or emphysema) have been associated with increased risk for lung cancer.[5,9,11,15]

- Family history of lung cancer has also been associated with increased lung cancer risk.[9,11]

- An association between husband's smoking status and family lifestyle has been reported.[16] Wives with husbands who were nonsmokers had better SES, were more conscientious housewives, ate better diets, had higher indices of family cohesiveness,

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and had better indices of overall health than did women married to smokers.

- At least one hobby, keeping pet birds, has been associated with increased lung cancer risk.[19]

Conclusion

While of general importance, the question of confounders appears to be particularly relevant in studies of Asian women. Certain cultural variables (e.g., use of smoky fuels, certain cooking methods, diet) differ greatly between Asian and Western populations. The potential effects of such factors must be considered when evaluating the results of epidemiologic studies on lung cancer incidence, particularly those considering ETS exposure. Table 1 presents a comparison and summary of Asian studies to date, revealing the increasing attention paid to confounders in these studies.

Dr. Linda Koo, in her 1988 paper on lifestyle correlates, summed up the importance of confounders as follows:

> [C]aution should be exercised when interpreting data on ETS. It may not be the hazards of tobacco smoke that are being evaluated, but a whole range of behaviors that result from having a smoking husband, which may in turn increase the risk for certain diseases among their wives and children.[16]

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Table 1a. Asian Studies Included in EPA Draft Risk Assessment: Epidemiologic Studies of Lung Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Hirayama, 1981, 1984 [Japan]	91,540	(+)	--	--	--	--
Chan and Fung, 1982 [Hong Kong]	223	(-)	--	Yes	--	--
Lam, 1985 [Hong Kong]	248	(-)	--	Yes	--	Home incense burning
Akiba, et al., 1986 [Japan]	1,385	(+)	--	--	--	Radiation exposure
Gao, et al., 1987 [Shanghai]	1,407	(-)	--	Yes	Yes	Medical history; hormonal factors
Koo, et al., 1987 [Hong Kong]	225	(-)	--	--	--	--
Lam, et al., 1987 [Hong Kong]	890	(+)	--	--	--	--
Geng, et al., 1988 [Tianjin, China]	314	(+)	Yes	--	--	Medical history; occupation
Inoue and Hirayama, 1988 [Japan]	83	(+)	--	--	--	--

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Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Shimizu, et al., 1988 [Japan]	180	(-)	Yes	--	Yes	Occupation

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported relative risk was not statistically significant.

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Table 1b. Asian Studies Published After EPA Draft Risk Assessment: Epidemiologic Studies of Lung Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
He, et al., 1990 [China]	536+	(-)	Yes	Yes	--	Medical history
Sobue, et al., 1990 [Japan]	639	(-)	Yes	--	--	--
Wang, et al., 1990 [NE China]	110	(-)	Yes	--	--	Indoor and outdoor air pollution
Wu-Williams, et al., 1990 [NE China]	1,924	(+)**	Yes	Yes	Yes	Medical history; occupation
Liu, et al., 1991*** [China]	221	(-)	Yes	Yes	--	Medical history

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported risk was not statistically significant.
\+ Males and females combined.
** The reported relative risk was statistically significantly negative.
***Full report on population discussed in He, et al., abstract.

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Table 1c. Ancillary Asian Studies, Not Considered in EPA Draft Risk Assessment

Study [site]	Sample Size	Factors Considered: Spousal Smoking	Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Koo, et al., 1984 [Hong Kong]	400	No**	--	--	--	--
Mumford, et al., 1987 [China]	--	No	Yes	--	--	--
Chapman, et al., 1988 [China]	144+	No	Yes	--	--	--
Koo, et al., 1988 [Hong Kong]	136	No	--	--	Yes	Lifestyle variables
Du and Ou, 1990 [China]	1,324	No	Yes	--	--	--
Xu, et al., 1990 [NE China]	1,077	No	Yes	Yes	Yes	Indoor and outdoor air pollution; occupation

** Other questions were asked regarding ETS.
+ Males and females combined.

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A selection of the relevant literature follows. Useful information is highlighted in yellow; problematic statements are highlighted in blue.

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REFERENCES

1. Rylander, R., "Environmental Tobacco Smoke and Lung Cancer," The New England Journal of Medicine 323(12): 834, 1990.

2. Katzenstein, A.W., "An Estimate of Adult Mortality in the United States from Passive Smoking: A Response," Environment International 16: 175-193, 1990.

3. Chen, B.H., Hong, C.J., Pandey, M.R. and Smith, K.R., "Indoor Air Pollution in Developing Countries," World Health Statistics Quarterly 43: 127-138, 1990.

4. Anonymous, "Lung Cancer in South China," Oncology Times 7(6): 33, 1986.

   deSerres, F.J. and Matsushima, T., "Meeting Report: Mutagenesis and Carcinogenesis by Nitropyrenes and Cancer Chemotherapeutics," Mutation Research 164: 3-8, 1986.

5. Geng, G.-Y., Liang, T.H., Zhang, A.Y. and Wu, G.L., "On the Relationship Between Smoking and Female Lung Cancer," Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 283-285.

6. Mumford, J.L., He, X.Z., Chapman, R.S., Cao, S.R., Harris, D.B., Li, X.M., Xian, Y.L., Jiang, W.Z., Xu, C.W., Chuang, J.C., Wilson, W.E. and Cooke, M., "Lung Cancer and Indoor Air Pollution in Xuan Wei, China," Science 235: 217-220, 1987.

7. Chapman, R.S., Mumford, J.L., Harris, D.B., He, X., Jiang, W. and Yang, R., "The Epidemiology of Lung Cancer in Xuan Wei, China: Current Progress, Issues and Research Strategies," Archives of Environmental Health 43(2): 180-185, 1988.

8. Du, Y.-X. and Ou, X.-L., "Indoor Air Pollution and Woman Lung Cancer," Indoor Air '90: Proceedings of the 5th International Conference on Indoor Air Quality and Climate, Toronto, Canada, July 29-August 3, 1990.

9. Liu, Z., He, X., and Chapman, R.S., "Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China," International Journal of Epidemiology 20(1): 26-31, 1991.

   He, X., Chen, W., Liu, Z. and Chapman, R.S., "An Epidemiological Study of Lung Cancer in Xuan Wei County, China: Current Progress," (abstract), presented at the Second Annual Meeting of the International Society for Environmental Epidemiology, Berkeley, California, August 13-15, 1990.

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10. Wang, F.-L., et al., "Analysis of Risk Factors for Female Lung Adenocarcinoma in Haerbin: Indoor Air Pollution," Chinese Journal of Preventive Medicine 23(5): 270-273, 1989 (translation).

11. Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, J., Fraumeni, J.F. and Henderson, B.E., "Lung Cancer Among Women in North-East China," British Journal of Cancer 62: 982-987, 1990.

12. Xu, Z.-Y., Blot, W.J., Xiao, H.-P., Wu, A., Feng, Y.-P., Stone, B.J., Sun, J., Ershow, A.G., Henderson, B.E. and Fraumeni, J.F., "Smoking, Air Pollution, and the High Rates of Lung Cancer in Shenyang, China," Journal of the National Cancer Institute 81: 1800-1806, 1989.

13. Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. and Tominaga, S., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku Journal of Experimental Medicine 154: 389-397, 1988.

14. Sobue, T., Suzuki, R., Nakayama, N., Inubuse, C., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwabara, O., Ichigaya, M., Kurata, M., Kuwabara, M., Nakahara, K., Endo, S. and Hattori, S., "Passive Smoking Among Nonsmoking Women and the Relationship Between Indoor Air Pollution and Lung Cancer Incidence -- Results of a Multicenter Case Controlled Study," Gan to Rinsho 36(3): 329-333, 1990 (translation).

15. Gao, Y.-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. and Fraumeni, J.F., "Lung Cancer Among Chinese Women," International Journal of Cancer 40: 604-609, 1987.

16. Koo, L.C., "Dietary Habits and Lung Cancer Risk Among Chinese Females in Hong Kong Who Never Smoked," Nutrition and Cancer 11: 155-172, 1988.

Koo, L.C., Ho, J.H.-C. and Rylander, R., "Life-History Correlates of Environmental Tobacco Smoke: A Study on Nonsmoking Hong Kong Chinese Wives with Smoking Versus Nonsmoking Husbands," Soc Sci Med 26(7): 751-760, 1988.

Koo, L.C., "Environmental Tobacco Smoke and Lung Cancer: Is It the Smoke or the Diet?" Present and Future of Indoor Air

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Quality, C.J. Bieva, et al., (eds.), (Amsterdam: Excerpta Medica, 1989): 65-75.

17. Tewes, F.J., Koo, L.C., Meisgen, T.J. and Rylander, R., "Lung Cancer Risk and Mutagenicity of Tea," Environmental Research 52: 23-33, 1990.

18. Sidney, S., Caan, B.J. and Friedman, G.D., "Dietary Intake of Carotene in Nonsmokers with and Without Passive Smoking at Home," American Journal of Epidemiology 129(6): 1305-1309, 1989.

Waller, K.D. and Smith, A.H., "Effects of Socioeconomic Status and Smoking on Serum Beta-Carotene," Archives of Environmental Health 46(2): 120, 1991.

19. Holst, P.A., et al., "For Debate: Pet Birds as an Independent Risk Factor for Lung Cancer," British Medical Journal 297: 1319-1321, 1988.

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there has been only one reported death from pneumocystis with concurrent saprophytic-mold pneumonia after myelosuppression from chemotherapy.[8] Potential contributing factors in this case included prednisone therapy, which decreases total T-cell counts when administered every six hours.[9] To our knowledge, concurrent cytomegalovirus and pneumocystis pneumonia have not been reported in any patient with chronic lymphocytic leukemia or as the result of corticosteroid therapy alone. Patients with chronic lymphocytic leukemia may be predisposed to a reduction in the CD4:CD8 ratio by the nature of their disease.[6,7] Fludarabine selectively depletes CD4 cells to alter this ratio further and may contribute to the generation of a clinical and immunologic picture similar to that of AIDS.

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1. Keating MJ, Kantarjian H, Talpaz M, et al. Fludarabine: a new agent with major activity against chronic lymphocytic leukemia. Blood 1989; 74:19-25.
2. Casper ES, Mittelman A, Kelson D, Young CW. Phase I clinical trial of fludarabine phosphate (F-ara-AMP). Cancer Chemother Pharmacol 1985; 15:233-5.
3. Vadhan-Raj S, Wong G, Gnecco C, et al. Immunological variables as predictors of prognosis in patients with Kaposi's sarcoma and the acquired immunodeficiency syndrome. Cancer Res 1986; 46:417-25.
4. Taylor JM, Fahey JL, Detels R, Giorgi JV. CD4 percentage, CD4 number, and CD4:CD8 ratio in HIV infection: which to choose and how to use. J Acquir Immune Defic Syndr 1989; 2:114-24.
5. Boldt DH, Von Hoff DD, Kuhn JG, Hersh M. Effects on human peripheral lymphocytes of *in vivo* administration of 9-β-D-Arabinofuranosyl-2-fluoroadenine-5'-monophosphate (NSC 312887), a new purine antimetabolite. Cancer Res 1984; 44:4661-6.
6. Hautekeete ML, De Bock RF, Van Bockstaele DR, Colpin GC, Berneman ZN, Peetermans ME. Flow cytometric analysis of T-lymphocyte subpopulations in B-cell chronic lymphocytic leukemia: correlation with clinical stage. Blut 1987; 55:447-52.
7. Semenzato G, Pezzutto A, Agostini C, Albertin M, Gasparotto G. T-lymphocyte subpopulations in chronic lymphocytic leukemia: a quantitative and functional study. Cancer 1981; 48:2191-7.
8. Reed AE, Body BA, Austin MB, Frierson HF Jr. *Cunninghamella bertholletiae* and *Pneumocystis carinii* pneumonia as a fatal complication of chronic lymphocytic leukemia. Hum Pathol 1988; 19:1470-2.
9. Hepburn B, Slade JD. Effect of divided daily dose prednisone therapy on circulating T cell subsets. J Rheumatol 1987; 14:19-22.

ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

To the Editor: There is much concern today over the relation between exposure to environmental tobacco smoke and lung cancer. Some 20 cohort and case–control studies have compared lung-cancer incidences in nonsmoking women married to smokers with those in nonsmoking women married to nonsmokers and reported risk ratios of up to 2. Several have reported dose–response relations, and others have shown increases, although not statistically significant ones.[1]

At this stage, a statistical association between exposure to environmental tobacco smoke and an increased risk of lung cancer should be accepted as real. However, the question of whether this association describes a causal relation is still open.

The biologic plausibility — an important methodologic requirement in epidemiologic studies of weak associations[2] — is rather low. Environmental tobacco smoke contains carcinogenic agents, but risk estimates are high in view of the relatively low doses received. Even at high levels of exposure, the doses may be only about 1/10 to 1/2 the dose received by someone actively smoking one cigarette.[3] Furthermore, the lung-cancer risk among nonsmoking women has not increased during the past decades, suggesting that environmental tobacco smoke does not add significantly to lung-cancer mortality among women.[4]

Studies of environmental tobacco smoke commonly compare risks in nonsmoking women married to smokers with those in nonsmoking women married to nonsmokers. The incidence of lung cancer in this population ranges from 3 to 14 per 100,000, with differences in the rates for various ethnic groups living in the same environment.[5] This suggests that environmental factors other than tobacco smoke influence the risk of lung cancer in this group — perhaps radon exposure[6] or food constituents.[7] There is also increasing evidence that certain factors in foods, particularly vegetables and fruits, protect against environmentally induced lung cancer. Differences in risk ratios of up to 5 have been found between smokers with and those without an adequate supply of vitamin A in the diet.[8]

If groups exposed to environmental tobacco smoke were selected either for exposure to other lung-cancer risk factors or for a lack of protective factors, exposure to environmental tobacco smoke would be confounded. This hypothesis is supported by two recent studies comparing dietary habits among nonsmoking women married to smokers and nonsmoking women married to nonsmokers: one found that the group married to smokers had a higher exposure to risk factors and a lower intake of protective factors,[9] and the other that this group had a lower intake of a specific protective factor — carotene (Sidney S, Caan BJ, Friedman GD: unpublished data).

In the nonsmoking female population, selection for those with a higher exposure to lung-cancer risk factors or a lower intake of protective factors would result in differences in lung-cancer rates of about 2, which is consistent with ratios that have been found for the risk of those exposed to their husbands' environmental tobacco smoke to the risk of those not exposed.[1]

Studies evaluating the hypothesis of a relation between exposure to environmental tobacco smoke and lung cancer must take into account other environmental risk or protection factors and the possibility that exposure to environmental tobacco smoke may be confounded. This has not been considered in the majority of such studies. Until this has been done, the claim of causality between environmental tobacco smoke and lung cancer remains uncertain.

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1. The health consequences of involuntary smoking: a report of the Surgeon General. Rockville, Md.: Department of Health and Human Services, 1986:1-359.
2. Workshop on guidelines to the epidemiology of weak associations. Prev Med 1987; 16:139-210.
3. Rylander R, Peterson Y, Snella M-C. ETS — environmental tobacco smoke: report from a workshop on effects and exposure levels, March 15–17, 1983, Geneva, Switzerland. Eur J Respir Dis 1984; 65:Suppl 133:1-152.
4. Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. J Natl Cancer Inst 1985; 75:463-9.
5. Hinds MW, Stemmermann GN, Yang H-Y, Kolonel LN, Lee J, Wegner E. Differences in lung cancer risk from smoking among Japanese, Chinese and Hawaiian women in Hawaii. Int J Cancer 1981; 27:297-302.
6. Committee on the Biological Effects of Ionizing Radiations, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council. Health risks of radon and other internally deposited alpha-emitters: BEIR IV. Washington, D.C.: National Academy Press, 1988.
7. Wynder EL, Hebert JR, Kabat GC. Association of dietary fat and lung cancer. J Natl Cancer Inst 1987; 79:631-7.
8. Bjelke E. Dietary vitamin A and human lung cancer. Int J Cancer 1975; 15:561-5.
9. Pisani P, Berrino F, Macaluso M, Pastorino U, Crosignani P, Baldasseroni A. Carrots, green vegetables and lung cancer: a case-control study. Int J Epidemiol 1986; 15:463-8.

SELECTED PSYCHOLOGICAL CHARACTERISTICS OF ANABOLIC–ANDROGENIC STEROID USERS

To the Editor: Although psychological and behavioral effects associated with the administration of anabolic–androgenic steroids were first noted 50 years ago,[1] recent reports suggest that affective and psychotic syndromes, some of violent proportions, may result from steroid use.[2,3] Cases have been reported in which the presumed psychological and behavioral effects of steroids are alleged to have substantially influenced the commission of criminal acts.[4,5] This

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LETTERS TO THE EDITOR

AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING; A RESPONSE

Dear Editor:

The health implications of environmental tobacco smoke (ETS) remain controversial. Neither the published reports nor statements from public health officials and agencies have resolved the question of ETS health effects, nor are they likely to in the near future.

A. Judson Wells' paper, "Estimate of Adult Mortality in the United States from Passive Smoking" (1988) is yet another effort to draw scientific verity from a reassessment of published epidemiological data. But this new look does not change the quality or meaning of the existing evidence, which remains equivocal. Neither does it substantively support the author's statement that exposure to ETS "can have adverse long term health effects that are more serious than previously thought".

The conclusions of nonsmokers' increased risk of lung cancer from ETS exposure found in the reports of the National Academy of Sciences (NRC 1986) and of the Surgeon General (USSG 1986) were based on epidemiological studies that produced a wide range of findings. The relative risk (RR) values summarized in Table 12.4 of the NAS report ranged from 0.50 to 3.25, with 17 out of 20 risk estimates (for subgroups by sex) lacking statistical significance. In seven additional reports since the NAS document was published, relative risk values ranged from "<1.00" to 1.65, with only the latter being statistically significant. The RR values from all 29 subgroups in the 20 studies included in the NAS report plus those published later are summarized in Table 1 herein.

All of the epidemiological studies that comprise the data base for estimating nonsmokers' risk of lung cancer in relation to ETS are actually estimates of association based on spousal smoking. In not a single study was either exposure to ETS or retained dosage determined. A few studies have attempted to estimate the degree of exposure to spousal smoking in terms of hours per day or total years of exposure, but none of the studies measured ETS exposure in objective and quantitative terms or even estimated ETS exposure with any degree of reliability. Proximity to a smoker sitting across the dining table does not permit an estimate of the nonsmoker's exposure to ETS, which will vary according to room volume, ventilation rates, the physical and chemical changes in ETS as it ages, and other factors that influence the concentrations and duration of ETS exposure. A spouse's smoking in another room or in another building can have even less or no significance at all in assessing the possible role of passive smoking on a subject's health.

It should be recognized, also, that association can never establish causality. At best, association can only suggest the possibility of causality. Feinstein (1988), discussing public alarms based on epidemiological studies, recently pointed out that "a causal suspicion is supported if an impressive statistical association appears in the 2 by 2 tabulation for subgroups of people reported as being exposed or nonexposed, diseased or nondiseased".

There are many ways to look at data and try to draw meaning from the aggregation of values. After deciding that the 13 studies which survived critical assessment did not, individually or collectively, support a definitive conclusion on the risk of lung cancer in relation to spousal smoking, the NAS Committee performed a meta analysis on the aggregated data, leading to an estimated risk increase of about 34% for nonsmokers married to smokers. This estimate has been questioned on a variety of grounds by a number of investigators (Letzel et al. 1988).

It can be argued that even if a first order relationship does not exist between disease and passive smoking in the epidemiological studies, the data used by Wells are the best evidence available. And it can be argued that even the array of values shown in Table 1 is not impressive in the sense that Feinstein specifies, there are other ways of testing the data, as has been done by Wells.

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Table 1. Statistical significance of risk values for lung cancer in relation to spousal smoking.

Investigator	Not Statistically Significant		Statistically Significant	
	Male	Female	Male	Female
*Chan and Fung (1982)		0.75		
*Buffler et al. (1984)	0.50	0.78		
Dalager et al. (1986)	<1.00			
*Kabat and Wynder (1984)	1.00	0.79		
Gao et al. (1987)		0.9 [a]		
*Gillis et al. (1984)		1.00		
*Lee et al. (1986)		1.00		
Gao et al. (1987)		1.1 [b]		
Shimizu et al. (1988)		1.1		
*Garfinkel (1981)		1.17[c]		
*Pershagen et al. (1987)		1.20		
Wu et al. (1985)		1.20		
*Lee et al. (1986)	1.30			
*Garfinkel et al. (1985)		1.31[c]		
*Akiba et al. (1986)	1.80	1.50		
*Koo et al. (1984)		1.64		
Brownson et al. (1987)		1.68		
Humble et al. (1987)	>1.20	1.80		
*Correa et al. (1983)	2.00	2.07[c]		
*Hirayama (1981)			2.25	1.63
Lam et al. (1987)				1.65
*Trichopoulos et al. (1981)				2.11
*Gillis et al. (1984)		3.25		

* Risk values from Table 12.4, National Academy of Sciences Report (1986)
a Exposure in adult life.
b Exposure in childhood.
c Statistically significant trends in one or more data subsets within the study.

There remains, however, the fundamental question of the quality of the individual underlying studies whose data are under consideration. Many of the epidemiological studies assessing the risk of lung cancer from spousal smoking have been criticized for a variety of methodological flaws and weaknesses, especially with regard to the potential for misclassification (Überla 1987; Balter et al. 1986; Lebowitz 1986; OTA 1986).

Misclassification of subjects is a source of error where patients claiming to be never smokers are in fact current or exsmokers. Wells conceded the likelihood of 5% misclassification. But misclassification of smoker status has been found at levels from 10% to 40% (Schwartz et al. 1988; Weiss 1988). NAS noted the likelihood of misclassification and lowered its estimate of the elevated risk to 25% from 34%, but it failed to indicate whether the lower value was statistically significant. (NAS found the combined risk from American studies a 14% increase, which was not statistically significant.)

Misclassification of disease can also be a source of error. There was a marked potential for misclassified disease in the studies having statistically significant risk ratios in the NAS and Surgeon General's reports. In Hirayama's study of Japanese women, his 1984 report suggests that only 21 of the 200 lung cancer cases (10.5%) were histologically confirmed, while the Surgeon General's report states that "none" were verified. Akiba et al. (1986) studying survivors of the Hiroshima and Nagasaki atom bombings, noted 43% of the lung cancer cases had not been histologically confirmed. Weiss (1988) notes that "thirteen percent of the cases [in Garfinkel's study] proved on review not to involve lung cancer".

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Misclassification of exposure can be a source of uncertainty in studies that attempt to find exposure-response relationships. There is little basis for considering estimates of spouses' smoking to be reliable. Pron et al. (1988) concluded that "test-retest estimates of reliability [over a six-month time span] would suggest that misclassification of such exposures may be extensive". Vogt (1977) found "twenty-two percent of persons gave different answers on the two questionnaires [on the number of cigarettes smoked per day] given about an hour apart".

Among the variety of flaws and weaknesses found in the various epidemiological studies on ETS and lung cancer, it is worth noting the age bias found by Ahlborn and Überla (1988) in Hirayama's study and their conclusion that "the risk increase ... disappears completely when one removes selection bias by age". Überla (1987), highlighting the weaknesses of the epidemiological studies comprising the NAS data base, had earlier concluded, "False plus false does not equal true."

In addition, most of the epidemiological studies have failed to take into account significant confounding factors in assessing lung cancer risk in relation to ETS. Many risk factors for lung cancer have been identified, including exposure to heavy metals, organic chemicals, combustion by-products, natural and man-made radiation, diet, and nutritional status, personal health history, emotional, and psychological factors. Holst et al. (1988) recently reported significantly increased risk in relation to keeping pet birds and to reduced vitamin C intake. Gao et al. (1987) found no significant increased risk for Chinese women in relation to passive smoking or type of employment but did find significantly increased risk in relation to previous lung disease, cooking practices, and shorter menstrual cycles, reflecting hormonal factors. Some of these factors may act independently, but many may interact. Any attempt to assess the role of one factor must take into account all other relevant factors.

None of the epidemiological studies on spousal smoking took into account confounding factors other than attempting to match cases with controls by age, residence, and general socio-economic status. Of the 20 epidemiological studies, those by Hirayama and by Lam et al. (1987) have the two largest number of lung cancer cases, with the increased risk in both being statistically significant. Both studies are of Oriental populations, which suggests that many factors like cooking practices and fuels for cooking and heating should have been controlled.

All of the studies included in Wells' Table 4, on which he based his estimate of heart disease deaths related to passive smoking, similarly fail to consider the confounding effect of the many cardiovascular disease risk factors that have already been established for that disease.

Some observers have commented that increased risk of lung cancer from ETS exposure seems implausible because the ETS components are so dilute in ambient air compared to the concentrations of these substances in mainstream smoke. In addition, it has been found that nonsmokers retain far less of inhaled ETS than active smokers retain of mainstream smoke. Wells noted that "smoke retention by a passive smoker is only about 1/400 that retained by a direct smoker in a 16 hour day". This is more than one order of magnitude greater than Rickert's calculation (1988) that nonsmokers exposed to ETS retain about 1/8000 the amount of particulate matter retained by the active smoker. Lee (1988) cited estimates of the same range: 1/5000 for males, 1/10 000 for females. All of these estimates are probably on the high side, since none of the studies appears to have considered the chemical and physical changes that occur as ETS ages and the losses of ETS through evaporation, fallout, and deposition over time.

Other observers have commented on the implausibility that lung cancer in nonsmokers might be caused by ETS. Aviado (1988) noted that none of 17 constituents of ETS "designated as suspect carcinogens ... [has] been adequately shown to cause pulmonary cancer via inhalation in animals". Crawford (1988) noted that "no atypical cellular changes have been found in the lungs of nonsmokers". Lee (1987) concluded "that exposure to smoke constituents of nonsmokers is too low to explain the moderate increase in risk of lung cancer seen in epidemiological studies in self-reported never smokers married to smokers. This increase in risk is much more plausibly explained by misclassification of smokers as nonsmokers than by a direct effect of passive smoking".

Wells has attempted to make his calculation of annual deaths from exposure to ETS appear more reasonable by comparing it to the larger estimate of Repace and Lowrey, but their estimate has been severely criticized because the controls were Seventh Day Adventists (SDA) whose life style is so radically different from that of the non-SDAs married to smokers that the comparison is considered inappropriate (OTA 1985; Balter et al. 1986; Überla 1987).

Taking these and other factors into account, Gostomzyk (1986) concluded, following the International Experimental Toxicology Symposium on Passive Smoking in Essen, FRG, that "even toxicology has not been able to ascertain with any greater degree

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of probability than did epidemiology that there exists a link between damage to health and passive smoking".

Perhaps it is the weight of these facts, interpretations, and opinions that caused no less an authority than the American Cancer Society to assert last year that "the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers..." (ACS 1988).

A final comment: both the title and the content of the editorial that accompanied the Wells paper suggests that the paper provides stronger evidence of risk of cardiovascular disease (CVD) for nonsmokers married to smokers than the paper in fact offers. In 1986, both the NAS and USSG reports noted the lack of convincing evidence of significant CVD risk from ETS exposure. More recently, Fielding and Phenow (1988) commented on papers reporting an association between ETS exposure and CVD risk, concluding that "no firm conclusion that a causal relation exists is yet warranted".

Wells' calculations with respect to CVD are based on data from epidemiological studies that have the same weaknesses as the lung cancer studies. There is, thus, no basis for greater confidence in his estimate of heart disease deaths in relation to ETS than his estimate of lung cancer deaths.

It is commendable that those who are not satisfied continue to seek more meaning from the data. But in an issue as serious as this, it is important to note when the data fail to meet the standards for scientific inference.

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REFERENCES

Ahlborn, W.; Überla, K. Passive smoking and lung cancer: reanalyses of Hirayama's data. In: Perry, R.; Kirk, P. W., eds. Indoor and ambient air quality. London: Selper Ltd.; 1988: p. 169-178.

Akiba, S.; Kato, H.; Blot, W. J. Passive smoking and lung cancer among Japanese women. Cancer Res. 46:4804-4807; 1986.

ACS (American Cancer Society). General facts on smoking and health; 1988 (p. 3).

Aviado, D. M. Suspected pulmonary carcinogens in environmental tobacco smoke. In: Perry, R.; Kirk, P. W., eds. London: Selper, Ltd.; 1988: pp. 141-146.

Balter, N. J.; Schwartz, S. L.; Kilpatrick, S.J.; Witorsch, P. Causal relationship between environmental tobacco smoke and lung cancer in non-smokers: a critical review of the literature. Proc. Air Pollut. Control Assoc. 86-80.9; 1986.

Brownson, R. C.; Reif, J. S.; et al. Risk factors for adenocarcinoma of the lung. Amer. J. Epidemiol. 125: 25-34; 1987.

Buffler, F. A.; Pickle, L. W.; Mason, T.J.; Contant, C.. The causes of lung cancer in Texas. In: Mizell, M.; Corread, P., eds. Lung cancer causes and prevention. New York: Verlag Chemie International Inc.;1984: p. 83-99.

Chan, W. C.; Fung, S. C. Lung cancer in nonsmokers in Hong Kong. In: Grundmann, E., ed. Cancer epidemiology, vol. 6. New York: Gustav Fischer Verlag; 1982: pp. 199-202.

Correa, P.; Pickle, L. W. Fontham, E.; Lin, Y.; Haenszel, W. Passive smoking and lung cancer. Lancet ii 2:595-597; 1983.

Crawford, W.A. Health effects of passive smoking in the workplace. In: Perry, R.; Kirk, P.W., eds. Indoor and ambient air quality, London: Selper Ltd., 1988:p. 203-210.

Dalager, N. A. et al. The relation of passive smoking to lung cancer. Cancer Res. 46:4808-4811; 1986.

Feinstein, A. R. Scientific standards in epidemiologic studies of the menace of daily life. Science 242:1257-1263.

Fielding, J. E.; Phenow, K. J. Health effects of involuntary smoking. N. Eng. J. Med. 319:1452-1460; 1988.

Gao, Y-T. et al. Lung cancer among Chinese women. Int. J. Cancer 40:604-609; 1987.

Garfinkel, L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J. Nat. Cancer Inst. 66:1061-1066; 1981.

Garfinkel, L; Auerbach, O.; Joubert, L. Involuntary smoking and lung cancer: a case-control study. J. Nat. Cancer Inst. 75:463-469; 1985.

Gillis, C. R.; Hole, D. J.; Hawthorne, P. Boyle, P. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur. J. Resp. Dis. (Supp. 133) 65:121-126; 1984.

Gostomzyk, G. J. Passivrauchen - Bericht Über ein internationales Symposium (23-25 Oktober 1986 Essen) Public Health 49: 212-215; 1987.

Holst, P. A.; Krombout, D.; Brand, R. For debate: pet birds as an independent risk factor for lung cancer. Brit. Med. J. 297:1319-1321; 1988.

Humble, C. G.; Samet, J. M.; Pathak, D. R. Marriage to a smoker and lung cancer risk. Amer. J. Public Health 77:598-602; 1987.

Hirayama, T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Brit. Med. J. 282:183-185; 1981.

Kabat, G. C.; Wynder, E. L. Lung cancer in nonsmokers. Cancer 53:1214-1221; 1984.

Koo, L.C.; Ho, J.H.C.; Saw, D. Is passive smoking an added risk factor for lung cancer in Chinese women? J. Exp. Clin. Cancer Res. 3:277; 1984.

Lam, T. H. et al. et al. Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. Brit. J. Cancer 56:673-678; 1987.

Lebowitz, M. D. The potential association of lung cancer with passive smoking. Environ. Int. 12:3-9; 1986.

Lee, P. N.; Chamberlain, J.; Alderson, M. R. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Brit. J. Cancer 54:97-105; 1986.

Lee, P. N. Passive smoking and lung cancer association: a result of bias? Human Toxicol. 6:517-524; 1987.

Lee, P. N. An alternative explanation for the increased risk of lung cancer in non-smokers married to smokers. In: Perry, R.; Kirk, P. W., eds. Indoor and ambient air quality. London: Selper Ltd.; 1988: p. 149-158.

NRC (National Research Council) Environmental tobacco smoke: measuring exposure and assessing health effects. Washington, D.C.: National Academy Press; 1986.

OTA (Office of Technology Assessment). Passive smoking in the workplace: selected issues. Washington, D.C.: Office of Technology Assessment, U.S. Congress; 1986.

Pershagen, G.; Hrubec, Z.; Svensson, C. Passive smoking and lung cancer in Swedish women. Amer. J. Epidemiol. 125:17-24; 1987.

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Pron, G. E.; Burch, J. D.; Howe, G.R.; Miller, A.B. The reliability of passive smoking histories reported in a case-control study of lung cancer. Amer. J. Epidemiol. 127:267-273; 1988.

Repace, J. L.; Lowrey, A. H. A quantitative estimate of nonsmokers' lung cancer risk from passive smoking. Environ. Int. 11: 3-22; 1985.

Rickert, W. S. Some considerations when estimating exposure to environmental tobacco smoke (ETS) with particular reference to the home environment. Can. J. Public Health 71:S33-S39; 1988.

Schwartz, S. L.; Balter, N. J. ETS-lung cancer epidemiology: supportability of misclassificant and risk assumptions. In: Perry, R.; Kirk, P.W., eds. Indoor and ambient air quality. London: Selper Ltd.; 1988: pp. 159-168.

Shimizu, H. et al. A case-control study of lung cancer in nonsmoking women. Tohoku J. Exp. Med. 154:389-397; 1988.

Trichopoulos, D.; Kalandidi, A.; Sparros, L.; MacMahon, B. Lung cancer and passive smoking. Int. J. Cancer 27:1-4; 1981.

Uberla, K. Lung cancer from passive smoking: hypothesis or convincing evidence? Int. Arch. Occup. Environ. Health 59:421-437; 1987.

USSG (U.S. Surgeon General) The health consequences of involuntary smoking: a report of the Surgeon General. DHHS (CDC) 87-8398. Washington, D.C.: U.S. Public Health Service; 1986.

Vogt, T. M. Smoking behavioral factors as predictors of risks. In: Research on smoking behavior. NIDA Monograph 17, National Institute of Drug Abuse, U.S. Public Health Service; 1977: pp. 98-110.

Weiss, S. T. What are the health effects of passive smoking? J. Resp. Dis. 9:46-62; 1988.

Wells, A. J. An estimate of adult mortality in the United States from passive smoking. Environ. Int. 14:249-265; 1988.

Wu, A. H.; Henderson, B. E.; Pike, M.C; Yu, M.C. Smoking and other risk factors for lung cancer in women. J. Nat. Cancer Inst. 74:747-751; 1985.

AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING; A RESPONSE

Dear Editor:

Wells (1988) estimates that exposure to environmental tobacco smoke (ETS) causes 46 000 deaths per year in the U.S.; 3000 from lung cancer, 11 000 from other cancers, and 32 000 from heart disease. These estimates are scientifically unjustified. Far too much faith is placed on results from often fragile epidemiological studies, with major sources of bias ignored or totally underestimated. In contrast, far too little faith is placed on evidence that nonsmokers have very much lower exposure to tobacco smoke constituents than do smokers, and that smokers are much more exposed to ETS than nonsmokers.

The evidence that exposure to ETS increases the risk of developing heart disease is extremely unconvincing. Of the studies cited by Wells, some are based on unacceptably small numbers of cases, e.g., Garland et al. (1985) where only two deaths occurred in women married to never-smoking husbands, while the only two studies with substantial numbers of deaths are both open to question.

When referencing the Japanese prospective study, Wells uses Hirayama's 1984 report of a statistically significant positive trend in wife's age-adjusted risk according to husband's smoking, but does not comment on the fact that, in 1981, Hirayama reported no association whatsoever. As shown in Table 1, the

Table 1. Female relative risks for heart disease from passive smoking in Japanese study.

Follow-up period	Total cases	Husband's smoking habit		
		Non-smoker	Ex or <19/day	20+/day
1966-79	406	1	0.97	1.03
1980-82[1]	88	1	2.85	5.07
1966-82	494	1	1.10	1.30

[1] Estimated from 1966-79 data (Hirayama 1981) and from 1966-82 data (Hirayama 1984). The 1984 paper provided relative numbers of deaths as 118, 240, and 136.

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INDOOR AIR POLLUTION IN DEVELOPING COUNTRIES

B. H. Chen,[a] C. J. Hong,[b] M. R. Pandey[c] & K. R. Smith[d]

Air pollution in general and indoor air pollution in particular have been associated in many people's mind with industrialization and urbanization and, thus, with the cities of developed countries where most of the measurements have been made. Recently, however, the UNEP/WHO Global Environment Monitoring System (GEMS)[e] has demonstrated quite convincingly that the worst ambient conditions reported today obtain in the cities of developing countries. In a similar fashion, although most studies of indoor air quality have been carried out in developed-country buildings, for many important pollutants the largest indoor-pollutant concentrations and exposures are also found in the developing countries in both rural and urban households.

Worldwide, there are four principal classes of indoor pollutants *(1)*, those derived from:

(i) combustion, e.g. carbon monoxide, particulates, and sulfur and nitrogen oxides from cooking stoves, space heaters and cigarettes (environmental tobacco smoke–ETS);
(ii) building materials, furnishings and chemical products, e.g. pesticides, volatile organic compounds, formaldehyde;
(iii) the ground under the building, i.e. radon;
(iv) biological processes, e.g. mold, mildew, mites.

As with ambient emissions, the impact of indoor emissions on concentrations depends directly on ventilation (airflow and mixing volume). In general, most housing in developed countries lies in temperate latitudes and thus has relatively low air exchange rates, i.e. typically one air change per hour or less. Under these conditions, even rather small emission rates can result in indoor concentrations that exceed those outdoors, considering also that indoor air quality is affected by outdoor levels. Since people spend a great proportion of time indoors, typically 90% or more, indoor pollution is frequently the predominant factor in total exposure.

In the developing world, however, much housing lies in tropical and subtropical regions and typically has much higher ventilation rates. In these circumstances, it takes fairly high emission rates to produce significant pollutant levels. Unfortunately, there seem to be many situations in which such strong indoor sources exist. Moreover, in spite of being a minority, several hundred million people in developing countries require space heating for a significant part of the year, and thus share with developed countries the difficult trade-off between space-heating fuel efficiency, ventilation and indoor air quality.

This review focuses on indoor combustion-derived pollutants, principally because comparatively little work has been published on the other three categories in developing countries. Although the main purpose is to review the available epidemiological studies, the relevant sources and pollutants will be briefly discussed first.

Indoor sources

Due to the generally higher ventilation rates, ETS has not been singled out in developing-country studies to date. With the alarming increase in smoking rates and the changing housing stock in some developing countries, however, such research may well be warranted. Although such minor combustion sources as incense and mosquito coils have occasionally been examined, most efforts have concentrated on cooking and heating stoves.

After tobacco, the most common indoor pollution source of concern in developed-country studies has been gas cookstoves. In the global context, however, gas stoves are near the upper end of an evolution in the quality of household fuels, sometimes called the energy ladder *(2)*. Although dependent on local conditions, at the lowest rung might lie those households that rely on dried animal dung and scavenged twigs and grass for cooking. The next step might be crop residues, followed by wood, and then charcoal. The first non-biomass fuel might be kerosene, as in India, or coal, as in China. Highest on the ladder lie bottled and piped gases and, for some rich communities, electricity. In general, each step involves an increase in the cooking system's levels of technology, cleanliness, efficiency and cost.

On a global scale, it is estimated that more than half of the world's households cook daily with unprocessed solid fuels, i.e. biofuels or coal. An unknown, but significant, proportion of this activity takes place in conditions where much of the airborne effluent is released into the living area. Although ventilation rates are often relatively high, the emission factors for such fuels are so great that indoor concentrations and exposures can be quite significant. Compared with gas stoves, for example, even stoves using one of the cleaner biofuels, wood, typically release 50 times more pollution in cooking an equivalent meal *(2)*.

Although less prevalent, space heating with unprocessed solid fuels can also lead to high indoor air-pollution levels. For part of the year in the high-altitude areas of developing countries in all four major regions (Asia, Africa, Latin America and Oceania), unvented space heating with biomass fuels is common. In addition, in much of temperate China,

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[e] Global Environment Monitoring System. *Assessment of urban air quality*. United Nations Environment Programme/World Health Organization, 1988 (Unpublished document).

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significant indoor concentrations result because of the high emission rates of coal fuels in simple stoves, although the pollution is less serious with venting, as is the case in most Chinese cities.

It is impossible at this point to derive a reliable estimate of the total developing-country population exposed to what might be termed "excessive" indoor concentrations, partly because there are few internationally-recognized standards for household concentrations. Assuming that they would be at least as stringent as outdoor standards, the total number of people exposed clearly rivals or exceeds that exposed to excessive ambient concentrations in all the world's cities,* i.e. several hundred million. Given the greater time spent indoors and the known magnitude of concentrations in many situations however, the total global dose-equivalent (amount actually inhaled) is probably higher for some important pollutants, e.g. particulates *(3)*. Pinpointing the actual sources of exposure is further complicated in many urban and even some rural areas, because indoor concentrations are influenced by outside as well as inside sources.

Pollutants

In spite of the long history of fascination with fire and hundreds of years of scientific effort, the ability to predict the detailed behaviour of combustion in any but the simplest configurations of fuel and air has eluded us. Nevertheless, empirical evidence has shown that unprocessed solid fuels produce hundreds of chemical compounds because of the incomplete combustion that occurs under the operating conditions of simple cookstoves, which are often little more than three-rocks or a small open-ended box of clay. Both coal and biomass act this way, although the mix of compounds from each is significantly different. Unlike coal, biomass generally contains few intrinsic contaminants, such as sulfur, trace metals and ash, and thus can, under proper conditions, be burned with no releases other than the products of complete combustion, i.e. carbon dioxide and water. Unfortunately, it has turned out to be difficult to reliably create these conditions in modestly-priced household devices.

As with tobacco smoke, which is also the result of open biomass combustion, such cookstove smoke is a complicated mixture of aerosol (droplets and solid particles) and gases. Biomass smoke contains significant amounts of several of the important pollutants, for which most countries have set standards: carbon monoxide, particulates, hydrocarbons and, to a lesser extent, nitrogen oxides. Perhaps more important however is that the aerosol contains many organic compounds that are thought to be toxic, carcinogenic, mutagenic or otherwise worrisome *(4)*. Coal smoke contains all this plus additional pollutants, e.g. sulfur oxides, inorganic ash particles and heavy metals such as lead. It is difficult to make generalizations about the relative amounts of each kind of pollutant however, because emissions can change with relatively small changes in fuel quality, configuration and combustion, and comparatively little detailed research has focused on such conditions.

*For a review of exposure studies related to biomass, see reference *(4)*; for those examining coal, see reference *(5)*.

Epidemiology

Although, by international comparison, the exposures received in households in many developing countries are large, epidemiological studies are still difficult. Expected short-term (acute) effects, such as acute respiratory infections (ARI), have many other important risk factors, some of which correlate with pollution exposures. Long-latency effects, such as cancer and chronic obstructive lung disease (COLD), also involve other risk factors. Moreover, it is difficult to associate these effects with previous exposures because of the long interval between these exposures and the onset of illness (the appearance of symptoms) *(5)*. Physiological and biochemical markers, such as lung function and immunological status, are only indicators of the particular pathology.

For the sake of conciseness this review focuses on developing-country studies published since 1980 and which include a health-related endpoint. Most of the early studies are cited, but not discussed in detail, and purely environmental studies are only mentioned occasionally, i.e. those that looked only at exposures.† The studies have been divided according to general category of source, biomass or coal, and the health-related endpoint being examined. Most have been done either in South Asia with rural populations using biomass, or in China with urban groups using coal.

Biomass – South Asia, Africa, Guatemala and Papua New Guinea

The vast majority of rural inhabitants in these parts of the world use unprocessed biomass fuels. Although significant in some communities, the utilization of these fuels in cities has been dropping as households move up the energy ladder, i.e. to kerosene and bottled gas. Proportionately, household coal use is minor, but it involves tens of millions of people and seems to be on the increase as the availability of biomass fuels dwindles and petroleum fuels remain relatively expensive.

Carboxyhaemoglobin (HbCO). In a study of carbon monoxide (CO) concentrations in 180 biomass-burning kitchens of two Guatemalan villages at different elevations (250 m and 1 350 m), Dary et al. *(7)* also determined HbCO blood concentrations in women. They found lower HbCO levels in women cooking in well-ventilated kitchens, but no difference in concentrations between houses having similar ventilation but situated at different altitudes.

In both well-ventilated and poorly-ventilated kitchens, however, there were higher HbCO levels in the higher-altitude village, with blood reaching 3.5% HbCO in some women as a result of concentrations of 30-50 ppm during the cooking period. In other words, at the same CO concentration, exposures at higher elevations produced higher HbCO levels, a finding consistent with known physiological mechanisms and a significant consideration in those many high-altitude areas of the developing world where solid fuels are burned for space heating without ventilation.

Lung function. To test for the effect of domestic smoke, Pandey et al. *(8)* used a dry portable spirometer to measure lung function in a random sample of 150 women aged 30-44 years living in a rural area on the outskirts of Kathmandu valley at an elevation

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of 1 600 m. The area is totally free from industrial and atmospheric pollution and women spend considerable time near the hearth, which is used for both cooking and heating. Smoke concentrations are high because dwellings are ill-ventilated and without chimneys. The selected sample comprised 6 groups of 25 subjects in each of 3 self-reported durations of daily smoke exposure for both smokers and non-smokers. All the spirometric tests (FVC, FEV1 and FMEF 25-75) were performed in the standard way recommended by the American Thoracic Society.

Variations in age, height, arm-span and weight between the three levels of exposure to domestic smoke in both the smokers and non-smokers were compared but no significant differences were found. There was a fall of mean FVC, FEV1 and FMEF 25-75, however, as duration of exposure increased. This decline was found to be statistically significant among the smokers but not among the non-smokers. Similar results were found after adjusting for age and height.

Respiratory symptoms. In Ahmedabad, western India, studies of the incidence of cough, cough with expectoration, dyspnoea and lung abnormalities found a statistically significant ($P < 0.05$) higher incidence among women cooking with smoky fuels *(9-11)*. The investigators also noted complaints by the women about the irritating effect of the smoke, particularly on the eyes.

In a three-year prospective study of clinical morbidity and air pollution in three areas of Bombay city and in one rural area nearby, Kamat et al. *(12)* found that the rural subjects were smaller in size, had lower lung function for their body stature and a higher incidence of cough and dyspnoea. Many of the respiratory symptoms exhibited by the rural population were similar to those of the moderately or severely polluted urban areas rather than the non-polluted areas. Use of wood for kitchen fuel is one of the explanations given by the authors for this finding.

In a study conducted in Ladakh, (Keith Ball, personal communication) a high prevalence of chronic respiratory symptoms was noted, particularly among women, which rises steeply with age to affect the majority of older people. About one-quarter of men and one-third of women over 50 have lung functions suggestive of obstructive airways disease, and this becomes worse in winter. Tobacco smoking has so far developed only in about 20% of the men but is virtually unseen in women. It has been suggested that domestic pollution, which is significant throughout much of the year in this high-altitude area, appears to play a part in creating this pattern.

Chronic obstructive lung disease. In a survey carried out in a housing complex in Chandigarh (India) and in a nearby village, a study was made of the records of 2 180 women aged over 20, working with different domestic fuels *(13)*. Sixty-six women (3%) had symptoms of chronic bronchitis, the highest number being in those who used the *chulla* (traditional unvented cookstove) for cooking. The cooking fuels were categorized in the following groups: I–liquefied petroleum gas (LPG); II–kerosene; III–coal; and IV–*chulla* (wood and cow dung). Five per cent of the subjects in group IV had chronic bronchitis compared to 1.5% and 1.3% in groups I and II, respectively. This difference was statistically significant ($P < 0.01$). Analysis of peak expiratory flow rate showed it to be low in subjects in group IV, but after adjusting for age and height, no difference was found between the four groups.

Hospital statistics in Nepal showed an unusually high proportion (46%) of *cor pulmonale* in hospital cardiac admissions *(14)*, indicating the need for field studies to determine the distribution and magnitude of chronic bronchitis and chronic *cor pulmonale*, and to identify the factors responsible *(15)*. Four sites were selected for this purpose: urban Kathmandu, nearby villages from Kathmandu Valley in the hills region, a village district in the plains region (terai) near India, and a district in the mountains. A survey of the prevalence of chronic bronchitis in the area of the hill villages was used to determine the required sample size in other areas. In the plains village, a simple random sampling method was used to select the sample. Two-stage random sampling was done in the urban areas and in the mountain district.

In all the study areas, houses were ill-ventilated and without chimneys. Most of the houses had only two or three rooms, but many had two floors. Cooking was done on traditional stoves in a corner of one of the ground-floor rooms in the morning and evening (the villagers take only two main meals a day). Most houses in the hills and mountains were customarily heated by means of an open fire in a fireplace known as an *ageno* dug into the floor of a ground-floor room. Members of the family sit around the *ageno* in the morning and evening to keep themselves warm. The *ageno* is also used for preparing cattle fodder in the morning and snacks for family members. Except in urban Kathmandu, there was no general industrial air pollution.

A questionnaire, modified slightly for different sites, recorded demographic information and exposure-related information such as smoking habits, location of kitchen, type of fuel used for cooking and heating and average time spent daily near the fireplace, along with the information required to diagnose chronic bronchitis according to the British Medical Research Council criteria. Emphysema and chronic *cor pulmonale* were diagnosed according to the WHO Expert Committee criteria. The individuals were classified as smokers, past smokers, or non-smokers and into various strata according to self-reported number of hours spent daily near the stove where, presumably, the highest smoke concentrations are found.

This study *(15)* found a high prevalence (crude and age-adjusted) of crude chronic bronchitis and *cor pulmonale* (10-30%). A striking feature was the similarity of rates in men and women. The difference in prevalence rate between the sexes was not statistically significant in any study area ($P > 0.10 - > 0.98$). This conflicts with most other studies, which have shown a lower prevalence rate among women. Tobacco smoking is common in both men and women in all but the urban area, where the smoking rate among women was only 14%. In all areas, however, women were light smokers (less than 10 cigarettes or equivalent per day). Heavy smoking among men was much more prevalent and the difference was statistically significant in all three rural areas ($P < 0.05 - < 0.001$) although not in urban Kathmandu. This suggests that the high prevalence of chronic bronchitis in women is primarily occupational since women engaged in cooking meals for the family are exposed for proportionately longer hours at higher concentrations of domestic smoke pollution than men. The difference in smoke

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exposure hours was significantly higher ($P < 0.001$) in women in all the study areas.

In the hill villages, a statistically significant ($P < 0.001$) positive correlation was found between prevalence of chronic bronchitis and exposure to domestic smoke pollution in both smokers and non-smokers *(Fig. 1)*. This supports earlier studies in India and Papua New Guinea *(16-19)* which suggested the possibility of a relationship between chronic bronchitis and domestic smoke pollution. The trend of increasing prevalence rates with increasing smoke exposure persisted even after elimination of the age effect *(20)*. A similar statistically significant correlation was also found in other study sites. In the mountain village, it was not possible to compare the prevalence between exposed and non-exposed groups, because everybody was exposed to domestic smoke from space heating. Unlike in other areas, however, many were exposed more than 8 hours per day. This provided an opportunity to test for an effect at longer hours of exposure. A significant correlation between bronchitis and smoke exposure was noted also beyond 8 hours of exposure among the smokers of both sexes. Hence, there seems to be a dose-response relationship between domestic smoke pollution and chronic bronchitis.

All the cases of chronic *cor pulmonale* identified in this study were complications of chronic bronchitis. Although most of the women smokers were light smokers, the study recorded similarity of prevalence of chronic *cor pulmonale* in the two sexes. This suggests that domestic smoke pollution is an important factor in producing *cor pulmonale*.

Childhood acute respiratory infections (ARI). Between 4 and 5 million children < 5 die in the world each year from ARI, mostly in developing countries. Most ARI studies have focused on the important issues of microbial causative agents, case-management with antibiotics, and effectiveness of vaccination. Research on risk factors has been judged to be of lesser importance in spite of the dominance of risk-factor reduction in the history of ARI control in the developed countries. Domestic smoke pollution has been assumed to be an important risk factor for ARI in many parts of the developing world,[1] but there have been few studies, particulary of the relationship with pneumonia, which is nearly always involved in fatal cases.

In a study carried out before 1980 in Papua New Guinea, Anderson *(21)* failed to find an effect of environmental differences, including household smoke, on acute respiratory symptoms among schoolchildren.

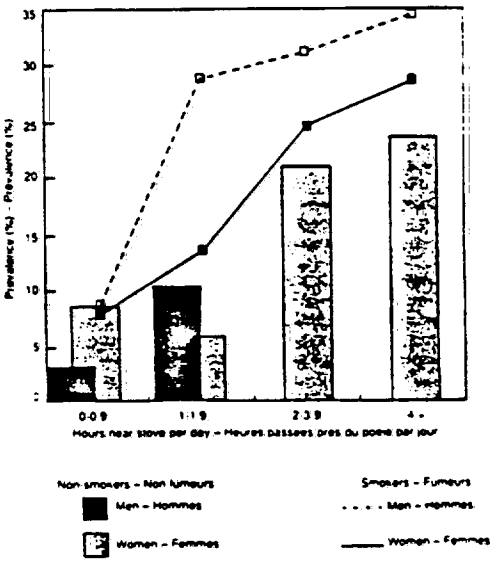
In a study of younger children in South Africa, Kossove *(22)* found that 70% of Zulu infants with respiratory symptoms lived in households with cookfire smoke, compared to 33% of a partially matched group who did not have such symptoms. This was significant at the $P < 0.005$ level, although there was no significant difference in the maternally-reported exposure times for the groups. No confounding factors were investigated.

[1] World Health Organization. *Acute respiratory infections in children*. Dossier ARI-5 of the Respiratory Infections Programme and the Programme Support Service. Geneva, 1987.

FIG. I

PREVALENCE OF CHRONIC BRONCHITIS IN NEPALESE HILL VILLAGES ACCORDING TO SELF-REPORTED DAILY TIME SPENT NEAR COOKING/HEATING STOVE, AROUND 1984 [a]

PREVALENCE DE LA BRONCHITE CHRONIQUE DANS LES VILLAGES NEPALAIS DE MONTAGNE EN FONCTION DU TEMPS PASSE PAR JOUR A PROXIMITE DU POELE (CUISINE/CHAUFFAGE), VERS 1984 [a]



[a] The strong associations are statistically significant ($p<0.001$) for all smokers and for women non smokers (20). – Une association nette est statistiquement significative ($p<0.001$) pour l'ensemble des fumeurs et pour les femmes qui ne fument pas (20).

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As part of WHO-sponsored indoor air pollution studies in Kenya and the Gambia *(23,*)*, ARI incidence in Kenyan children < 5 was monitored bi-weekly in 36 houses for 42 weeks. During this period, stationary indoor 24-hour monitoring was conducted twice in each house, for nitrogen dioxide and suspended particulates. Although respirable particulate concentrations were quite high (mean of 1.4 mg/m³), no correlation was found between ARI incidence and indoor concentrations of either pollutant, or with exposures of the children, as determined from the concentrations and time spans constructed by interviewing the mothers.

Moreover, the measured concentrations were quite homogeneously distributed among the households. Indeed, the intra-household variation between the two measurement days was greater than the inter-household variation, although households were randomly chosen from four groups stratified on the basis of house characteristics, roof type and kitchen arrangement, thought to influence ventilation, and thus indoor air quality. As the authors point out, given the apparent lack of natural variation in exposure among households, it would be quite difficult to establish smoke as a risk factor with this type of study design.

In the Gambia, on the other hand, where indoor woodsmoke levels were also high, but homogeneously distributed, there seemed to be significant differences in exposures because some young children are carried on their mother's back during cooking. Based on a multiple logistic regression, Campbell et al. *(24)* report an adjusted odds ratio of 2.8 for episodes of breathing difficulty among 280 children carried by their mothers. The only other significant risk factor was paternal smoking.

A semi-quantitative epidemiological study was conducted in Nepal by Pandey et al. *(25)*, to assess the relation between maternally-reported hours spent per day near the hearth by infants and children < 2, and episodes of life-threatening, moderate and severe ARI. In the study area, a hill region of Nepal, traditional stoves burning biomass fuels, mainly wood and crop residues, are used for cooking and heating in unventilated houses with no chimneys. The area is totally free from industrial pollution.

The first substudy was conducted during a six-month period in 1984. A statistically significant ($P < 0.01$) association was found when the exposed group was compared with the non-exposed in the two age strata i.e. < 1 year *(Fig. 2a)* and 1-2 years. In order to confirm and validate the findings, an additional three-month substudy was conducted in the same population. This substudy employed separate groups of observers to determine ARI episodes and smoke exposure times, thereby assuring a greater degree of independence in observation of the two variables. A statistically significant ($P < 0.01$) association was found in this second substudy as well *(Fig. 2b)*.

There were no obvious confounding factors that might account for these findings. Socioeconomic condition is not an important factor as more than 98% of the population live within a subsistence economy, and nearly all the houses are similar in construction. This preliminary study seems to suggest that domestic smoke pollution is a risk factor of ARI. As with all available studies, however, there were insufficient resources to fully monitor exposure, measure and correct for confounding variables, and to conduct the many expensive and time-consuming quality-control procedures needed for full-scale modern environmental epidemiology investigations.

Coal – East Asia

In China, coal is and will remain for decades the main energy source. Particulates and sulfur oxides emitted from coal combustion are two of the main urban atmospheric pollutants. In Shanghai, some 5% of total coal consumption is used for domestic cooking, making it the most important urban cooking fuel. For example, until 1987 Tianjin was the only city where all the families used gas stoves and in Beijing, only 70% of the families used gas or liquefied petroleum gas, while in Shanghai about half of the population use coal-cake stoves. Little indoor air quality research has been done in rural areas where most of the population uses crop residues and wood.

Research on indoor pollution and its health effects was initiated in China towards the end of the 1970s and over 100 papers have been published *(6)* on the subject. A series of epidemiological surveys have been carried out to evaluate the effect of indoor pollution on human health. In contrast to studies in developed countries, the gas-user group is usually considered as the unexposed control group, and the coal-user group as the exposure group.

Immunological function. The influence of indoor air pollution on immunological function was investigated in groups of primary-school students aged 10-13 exposed (or not) to coal smoke at home and at school *(26)*. Compared to the control group, the amount of SIgA in saliva of the exposure group decreased by 32.5%, and the activity of lysoenzyme by 17.3%. There were no differences in distribution of age, sex and ETS exposure between the groups (P values, all > 0.05).

Wang & Chen monitored the immunological parameters of primary-school pupils from families using different fuels for cooking.* The results were statistically significant (< 0.05) for white blood-cell count (mean reduction: 13%), saliva lysoenzyme (13%), transfer of lymphocyte (50%), IgG (29%), IgM (28%) and IgA (54%), but not in the PHA skin test.

Carboxyhaemoglobin (HbCO). The blood HbCO concentration in women using coal stoves was 2.1 ± 0.9%, compared to those using gas stoves at 1.4 ± 1.0% ($P < 0.01$). Women using coal stoves without chimneys had 4.3%, while those using chimneys had 3.0% *(27)*.

A study by Hu & Liu of 450 suburban schoolchildren < 13 near Beijing *(28)* found significantly higher HbCO levels in those living in traditional housing where pit stoves were used for heating and cooking, compared to those residing in modern buildings with stoves and chimneys. At 4.1% and 2.8%, however, both groups were high. The authors compare

* World Health Organization. *Indoor air quality in the Basse area, the Gambia.* (Document GEMS/HEALS WHO/PEP/88.3, 1988).

* Wang, J. & Chen, B. H. *[The influence of air pollution on immunological parameters of children].* Shanghai Medical University, 1987. (Graduate thesis). (In Chinese).

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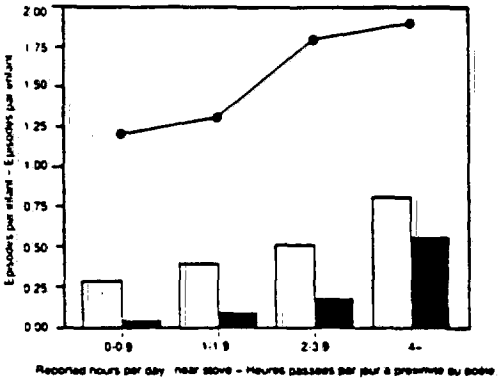
FIG. 2

ACUTE RESPIRATORY INFECTIONS IN INFANTS (0-1) IN THE HILL REGION OF NEPAL LISTED BY SEVERITY AND MATERNALLY REPORTED DAILY TIME NEAR STOVE [a]

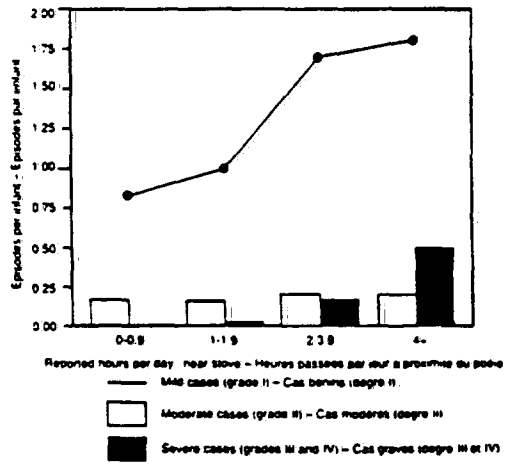
INFECTIONS RESPIRATOIRES AIGUËS CHEZ LES NOURRISSONS (0-1 AN) DANS LA RÉGION DE MONTAGNE DU NEPAL, CLASSÉES SELON LA GRAVITÉ ET SELON LE TEMPS PASSÉ PRÈS DU POÊLE CHAQUE JOUR AU DIRE DE LA MÈRE [a]

A. Based on six months' data collected in 1984 (233 infants) – Sur la base des données recueillies en 1984 sur une période de six mois (233 nourrissons)



Reported hours per day near stove – Heures passées par jour à proximité du poêle

B. Based on three months' data collected in 1989, with the same population (247 infants) but with separate teams diagnosing ARI and determining exposure – Sur la base des données recueillies en 1989 sur une période de trois mois dans la même population (247 nourrissons), des équipes distinctes étant chargées de diagnostiquer les IRA et de déterminer l'exposition



[a] The trends are significant in both cases (P) – Les tendances sont significatives dans les deux cas (P)

these results with an earlier urban study,[1] where HbCO levels of 4.3%, 3.0% and 1.1% were found for residents in homes heated by stoves without flues, by stoves with flues, and by circulating hot water respectively. This study also found other effects. There were significant differences in the incidence of lower respiratory diseases among girls ($RR = 3$, $p < 0.05$) but not for boys nor for upper respiratory diseases. Small or non-significant differences were found for immune and eye responses and lung function, after correcting for height, age, weight, family income and parental smoking *(28)*.

[1] Chang X. M. *[An epidemiological study on indoor air pollution]*. Second National Conference on Environmental Health, October 1984, Nanjing. (In Chinese).

Although small-scale combustion of all coal and biomass fuel is often associated with high CO emissions, poor combustion of all unprocessed biomass and high-volatile coals also emits large amounts of hydrocarbon aerosol and gas, e.g. aldehydes. Although these may have long-term health effects because of the intense irritation they cause, they act in the short term to warn when CO concentrations approach acutely toxic levels. In other words, it is extremely rare for someone to die from acute CO poisoning from such fuels. Even though measured CO concentrations can sometimes approach dangerous levels, the irritation due to hydrocarbons will awaken householders and prompt them to escape or open a window *(4)*.

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Unfortunately, this is not the case with the three principal low-volatile solid fuels: charcoal, naturally low-volatile coal such as anthracite, and processed (devolatilized) coal. These may release no more CO than the high-volatile solid fuels, but they do so with little of the irritating hydrocarbons that provide warning. As a result apparently, hundreds if not thousands of people die every year in northern China, Korea, the Islamic Republic of Iran and other developing countries where overnight space heating is provided by such fuels (mainly coal), along with excessive leakage of combustion gases into living areas, compounded by poor household ventilation. A study in Korea, for example, has shown a strong seasonal variation in hospital admissions for CO poisoning, peaking during the cold season where heating is used *(29)*. Mortality is not the only effect–high, but sublethal, exposures can cause serious poisoning.

Lung function. Li & Hong[a] monitored the lung functions (FVC, FEV1, FEV1%) of 213 women aged 50-70 years, including 167 women using coal and 46 using gas for cooking. Even after adjustment for potential confounding factors, i.e. age, body weight, height and ETS, there was a statistically significant difference between the coal group and the gas group in all lung functions tested.

In another study, the FEV1/FVC of persons using coal stoves was lower than those using gas stoves, while the reverse relationship was found for MEF25, MEF50 and MEF75. This was possibly due to higher NOx concentrations in homes using gas.

In Xuanwei County, Yunnan Province (southern China), the airway resistance of farmers and schoolchildren in homes where poor-grade bituminous coal was used for cooking was higher than in homes where wood and straw were used for cooking ($P < 0.001$) *(30)*.

Respiratory symptoms and non-cancer respiratory diseases. There seems to be an increase in respiratory symptoms and prevalence of respiratory diseases in coal-using families. A study[b] was conducted in two areas of Shanghai with populations of about 77 000 and 17 000 respectively. Two samples were selected, using cluster sampling: 1 316 using coal-cake stoves and 721 using gas stoves. The respiratory symptoms and prevalence of respiratory diseases were found to be 79% and 44%, respectively, for people using coal stoves and gas stoves ($P < 0.05$).

The prevalence of respiratory diseases among housewives aged 40-65 are 50% and 40%, respectively, for coal-using homes and gas-using homes, where $P < 0.05$, and relative risk for coal-using housewives is 1.9 *(28)*. The prevalence of common cold among persons using stoves with or without chimneys were 22% and 52% respectively; RR = 2.0 (without chimney), attributable risk = 25% *(31)*. The prevalence of chronic bronchitis, emphysema, cough, productive cough and breathlessness in women using coal stoves were significantly higher than among those using gas stoves. There were no significant differences in the prevalence of coronary heart disease, hypertension and a tight feeling in the chest between the coal- and gas-using groups.[c]

Another study,[m] carried out in Shanghai on 12 037 people, using the American Thoracic Society DLD-78 questionnaire, found that in areas where atmospheric pollution was light, the prevalence of COLD was 9.6% in the gas-user group and 15.6% in the coal-user group. In heavily-polluted areas, these prevalences were 12.8% and 17.3%, respectively. Multivariate analysis indicated that indoor air pollution had a stronger impact than outdoor air pollution.

Another survey of respiratory symptoms and diseases was carried out among retired women and nonemployed women aged 45 years and over *(32)*. Of the 393 women who responded to the questionnaire, 186 used gas for cooking and 207 coal. Indoor pollutant concentrations typically found in each type of home were determined, based on small representative samples. The results are listed in *Table 1*.

In order to determine whether factors other than indoor pollution (such as age, living standard, education, ETS, kitchen style and living space per person) were important influences, a multifactor logistic regression analysis was conducted. The result showed that domestic smoke was an important contributing factor to chronic bronchitis, emphysema,

[a] Li, L. & Hong, C. J. *[Kitchen air pollution and its health effects]* Shanghai Medical University, 1988 (Graduate thesis) (In Chinese).

[b] Lin, H. S. et al. *[Relation of air pollution and human health in a higher density residential area of Shanghai]*. Symposium on Environmental Health, Taiyuan, 1983. (In Chinese).

[c] Hong, C. J. et al. *[Studies on air pollution and its impact on health in Shanghai]*. Shanghai Medical University, 1989. (In Chinese).

TABLE 1. PREVALENCE OF RESPIRATORY SYMPTOMS AND DISEASES IN WOMEN USING DIFFERENT FUELS FOR COOKING, 1985

TABLEAU 1. PRÉVALENCE DES SYMPTÔMES ET MALADIES RESPIRATOIRES CHEZ LES FEMMES UTILISANT DIFFÉRENTS TYPES DE COMBUSTIBLES POUR LA CUISINE, 1985

Disease or symptom Maladie ou symptôme	Gas user group (186 cases) Groupe utilisant le gaz (186 cas) Number — Nombre	 %	Coal user group (207 cases) Groupe utilisant le charbon (207 cas) Number — Nombre	 %	$\chi^2(M-H)$ Number — Nombre	P %
Asthma — Asthme	6	3.3	15	7.2	2.2	>0.05
Chronic bronchitis — Bronchite chronique	22	11.8	51	24.6	7.5	<0.01
Bronchodilatation	3	1.64	13	6.23	4.6	<0.05
Emphysema — Emphysème	4	2.15	21	10.1	7.3	<0.01
Coronary heart disease — Cardiopathie coronarienne	27	14.5	25	12.1	0.69	>0.05
Hypertension	60	32.3	66	31.3	0.03	>0.05
Cough — Toux	33	17.7	83	40.1	19.1	<0.01
Expectoration	24	12.9	53	25.6	7.5	<0.01
Chest tightness — Gêne respiratoire	55	29.6	77	37.2	2.1	>0.05
Shortness of breath — Essoufflement	18	9.68	53	25.6	13.4	<0.001

Source: Reference (32) — Référence (32).

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bronchodilatation, cough, expectoration and shortness of breath. These conditions were 1.8-4.5 times more common among the group exposed to coal smoke. No significant difference was found for coronary heart disease.

In Hong Kong, Koo et al. *(33)* found small (10-20%) but statistically significant differences in nitrogen dioxide exposure levels as well as reported respiratory symptoms (allergic rhinitis and bronchitis) among non-smoking mothers in homes using piped gas (lower exposure) for cooking, compared to those using kerosene or bottled gas. A similar effect was found for incense-burning and kitchen ventilation, but not for mosquito coils or ETS. No effect was found in children.

Cancer. **Although the lung-cancer risks of occupational exposures as well as active smoking, and to a lesser extent ETS, have been extensively documented,** the relation between lung cancer and ambient air pollution remains uncertain. Indoor pollution, however, is now starting to be linked to lung cancer, especially among women cooking over coal-fired stoves, although their level of cigarette smoking and occupational exposure is much lower than men's.

Xu et al. *(34)* analysed female lung-cancer prevalence in 16 Chinese metropolitan areas, each with a population over 500 000 and located at various latitudes. They found that the correlation coefficients between female lung-cancer prevalence and latitude were statistically significant. The higher the latitude, the higher the lung cancer prevalence.

Yang et al.* compared several factors with the high and low lung-cancer prevalence regions in Wuhan (standardized rates: 26 vs. 12 per 100 000) to find that there were significant differences in stove types and density, sulfur dioxide and nitrogen oxides, but not for carbon monoxide.

In Guangzhou, there were 349 housewives among 1 243 female lung-cancer deaths *(35)*. These women (28%) had no previous occupational exposure, 40% of them were non-smokers, and none seemed to be exposed to significant outdoor air pollution. The epidemiological survey showed that female lung-cancer occurrence was related to exposure to coal combustion and cooking *(36)*. The investigators monitored kitchens for suspended particulates, deposited dust, and benzo(a)pyrene in deposited dust. They found (as expected) that concentrations were much higher in kitchens using coal compared to those using liquefied petroleum gas for cooking.

Based on a case-control analysis of 662 deaths (446 males and 216 females), the lung-cancer odds ratio (OR) of smoking and cooking was analysed and is presented in *Table 2 (36)*. Exposure to cooking was found to be an important contributing factor to female lung cancer, but not to male lung cancer. **The combination of smoking and cooking exposure has a synergistic effect on the prevalence of lung cancer in both males and females.**

Another matched case-control study and measurement of indoor air pollution was carried out in a northern Chinese city (Harbin) to analyse risk factors for female lung adenocarcinoma *(37)*. The results showed that a high coal-consumption index (HCCI, OR = 10.6), indoor smog pollution in winter (OR = 15.2) and low ceiling height of the living room (OR = 12.5) were the main risk factors for female lung adenocarcinoma. It was further confirmed by indoor air monitoring that the average air concentrations of total suspended particulates (TSP) and benzo(a)pyrene in bedrooms in winter were 4.4 and 27 times higher than the respective maximum allowable air concentrations in China. No significant correlation was found between female lung adenocarcinoma, and cigarette smoking and ETS.

TABLE 2. LUNG-CANCER ODDS RATIO (OR) OF SMOKING AND COOKING — CASE-CONTROL ANALYSIS, 662 PAIRS, 1988

TABLEAU 2. ODDS RATIO (OR) DE CANCER DU POUMON PAR EXPOSITION AU TABAC ET AUX FUMÉES DE CUISINE — ANALYSE CAS-TÉMOINS, 662 PAIRES, 1985

	M OR	P	F OR	P
(1) S+NS+E+NE[a]	1.0		1.0	
(2) NS+NE	0.31	>0.05	0.31	>0.05
(3) S+NE	4.4	<0.01	0.6	>0.05
(4) NS+E	1.4	>0.05	3.1	<0.05
(5) S+E	4.2	<0.01	5.8	<0.01

[a] S = smokers — fumeurs.
NS = non-smokers — non-fumeurs.
E = exposed (coal stove) — exposés (cuisinière à charbon).
NE = non-exposed (gas stove) — non exposés (cuisinière à gaz).
Source: Reference (36) — Référence (36).

In another Xuanwei study, the standardized lung-cancer mortality in 1973-1975 was 26 per 100 000, higher than the average urban lung-cancer mortality in China. In Xuanwei, lung-cancer prevalence was different in various regions, the highest being over 150 per 100 000, while the lowest was under 1 per 100 000, a difference of about a factor of 200. Although rare today, in the recent past high-tar bituminous coal burned in open pits was the main domestic fuel used in high lung-cancer prevalence regions, while anthracite coal and wood were used in low-prevalence regions. The prevalence of lung cancer in farmers was higher than among people in other occupations and there was little difference between sexes. This evidence suggests the presence of a strong carcinogenic factor linked to lung cancer in nonemployed women *(38)*. Research involving indoor air monitoring, epidemiological studies and animal exposure tests *in situ* have been conducted by the Chinese Academy of Preventive Medical Sciences and local public health and anti-epidemic stations with assistance from the United States Environmental Protection Agency *(39, 40)*.

In Hong Kong, however, no significant association was found between lung cancer and cooking fuels *(41)* or ETS *(42)*. The indoor-pollutant concentrations were much less than those found in the above-mentioned lung-cancer studies in China. Although there have been reports linking domestic smoke with the high rates of nasopharyngeal cancer among southern Chinese populations *(43, 44)* and in other groups, e.g. Kenya *(45, 46)*, most reviews have concluded that the risk must be small or non-existent compared to risk factors such as diet *(47)*.

Fluorosis. Increased fluorosis induced by high concentrations of fluoride in indoor air and food originating from coal combustion has been reported recently *(48-51)*. In the suburbs of Xiangtan (Hunan Province) the fluoride concentration in drinking-water was less than 1 mg/litre, but in coal it was

* Yang, X. et al. *[The relation of indoor air pollution and human health — a primary study]*. Workshop on Chinese environmental health, 1983. (In Chinese).

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190-330 mg/kg. Fluoride concentration originating from coal combustion was 0.018-0.066 mg/m³ in indoor air and 1.9-3.3 mg/kg in vegetables. The prevalence of dental fluorosis there was as high as 35% in residents of all ages. In a neighbouring area, the prevalence of dental fluorosis in a control group cooking with wood was only 4.9% *(48)*.

In the suburb of Luoyang (Henan Province) the fluoride concentration of coal was 370-640 mg/kg, and the indoor-air fluoride concentration was measured at 0.016 mg/m³. The vegetable and grain fluoride concentration was 0.95-3.4 mg/kg. This increased to 2.7-14 mg/kg after a half-year storage period indoors. There were 1 486 persons suffering from fluorosis among 2 246 persons aged over 6. The prevalence rate was 66% *(49)*. Increased prevalence of fluorosis due to coal combustion in residents has also been found in Xianwen (Sichuan Province), Ankang (Shanxi Province), Benxi (Liaoning Province) and Huanggang (Hubei Province).

Stroke. A group of 957 men were followed for 12 years in a study of risk factors for heart disease and stroke carried out in Shanghai *(52)*. During the study period, 24 subjects died. In addition to high blood pressure, age and smoking, the study found exposure to household coal smoke to be a significant risk factor. A dose-response relationship was found with the relative risk of heavy exposure (only coal use) of nearly 11, after correction for the other major risk factors. The slight-exposure groups (using both gas and coal) had a relative risk of nearly 4.

Conclusion

Available evidence in the developing world would seem to argue strongly that indoor air pollution from cook-fire smoke is a risk factor for chronic lung disease in adults, particularly women, and acute respiratory disease in young children. In addition, coal smoke may be an important risk factor for lung cancer in women. The total number of people exposed to high concentrations of smoke is likely to be several hundred million.

However, too few resources have been allocated to such studies for it to be possible to quantify these effects. Such efforts are needed, however, in order to determine the effectiveness of smoke-exposure reduction measures in comparison with other approaches for preventing or mitigating these diseases.

In particular, there is a need to link detailed epidemiological study designs using internationally accepted diagnostic procedures with detailed and systematic exposure determinations. This is not easy to do with cancer and chronic obstructive lung disease, since exposure histories going back several decades must be established.

One of the highest priorities for indoor air pollution epidemiology is to initiate a study of the risk factors for ARI, because of its importance as a cause of early childhood morbidity and mortality in many developing countries, and in view of the high indoor exposures that seem to prevail in many areas. A longitudinal intervention study lasting at least two years and including all seasons before and after intervention would most likely lead to results that are scientifically sound and useful for designing large-scale intervention programmes *(53)*.

A growing trend among those concerned with environmental epidemiology is the realization that, in order to understand the impact of pollution on health, it is necessary to monitor dwelling places rather than just the ambient environment. Total exposure assessment is the term for such efforts, which are beginning to reveal important sources and control measures different from those on which past efforts have focused *(4)*. Indeed, from a global standpoint, the present balance of research, monitoring and control efforts in air pollution should perhaps be shifted towards households using unprocessed solid fuels, which is where the largest number of susceptible persons can be found.

SUMMARY

Of the four principal categories of indoor pollution (combustion products, chemicals, radon and biologicals), research in developing countries has focused on combustion-generated pollutants, and principally those from solid-fuel-fired cooking and heating stoves. Such stoves are used in more than half the world's households and have been shown in many locations to produce high indoor concentrations of particulates, carbon monoxide and other combustion-related pollutants. Although the proportion of all such household stoves that are used in poorly ventilated situations is uncertain, the total population exposed to excessive concentrations is potentially high, probably several hundred million.

A number of studies were carried out in the 1980s to discover the health effects of such stove exposures. The majority of such studies were done in South Asia in homes burning biomass fuels or in China with coal-burning homes, although a sprinkling of studies examining biomass-burning have been done in Oceania, Latin America and Africa.

Of the health effects that might be expected from such exposures, little, if any, work seems to have been done on low birthweight and eye problems, although there are anecdotal accounts making the connection. Decreased lung function has been noted in Nepali women reporting more time spent near the stove as it has for Chinese women using coal stoves as compared to those using gas stoves. Respiratory distress symptoms have been associated with use of smoky fuels in West India, Ladakh and in several Chinese studies among different age groups, some with large population samples. Acute respiratory infection in children, one of the chief causes of infant and childhood mortality, has been associated with Nepali household-smoke exposures.

Studies of chronic disease endpoints are difficult because of the need to construct exposure histories over long periods. Nevertheless, chronic obstructive lung disease has been associated with the daily time spent near the stove for Nepali women and found to be elevated among coal-stove users compared to

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gas-stove users in Shanghai. In contrast to early reports, there seems to be little or no risk of nasopharyngeal cancer from cookstove smoke. Several studies in China, however, have found smoke to be a strong risk factor for lung cancer among non-smoking women. In addition, severe fluorosis has been observed in several parts of China where coal fluoride levels are high.

The high indoor concentrations and the potentially large (also poor and thus vulnerable) populations at risk, argue for more resources to be devoted to epidemiological studies of large numbers of exposed populations, using appropriate quality-control measures in order to generate reliable quantitative dose-response information. In the meantime, however, enough is known to warrant household, community and government efforts to reduce exposures through education and introduction of improved stoves, cleaner fuels and enhanced ventilation.

RÉSUMÉ

Pollution de l'air à l'intérieur des habitations dans les pays en développement

Des quatre principaux types de pollution à l'intérieur des habitations (produits de combustion, substances chimiques, radon et substances biologiques), la recherche dans les pays en développement a privilégié les produits de combustion et notamment les polluants résultant de l'utilisation de combustibles solides pour la cuisson et le chauffage. Les poêles incriminés sont en service dans plus de la moitié des habitations du monde et il a été prouvé en de nombreux endroits qu'ils étaient à l'origine de concentrations élevées de matières particulaires, d'oxyde de carbone et d'autres polluants liés à la combustion. Bien que l'on ne connaisse pas avec précision la proportion de poêles ainsi utilisés dans des locaux mal aeres, le nombre total de personnes exposees à des concentrations excessives de polluants est élevé, probablement plusieurs centaines de millions.

Dans le courant des années 80, plusieurs études ont été consacrées aux effets sur la santé de l'exposition à ces produits de combustion. La plupart ont été conduites en Asie méridionale dans des habitations où sont utilisés des combustibles tirés de la biomasse ou en Chine là où l'on utilise du charbon, bien que certaines études sur l'utilisation de la biomasse aient été faites en Océanie, en Amérique latine et en Afrique.

Parmi les effets de ce type de pollution qui peuvent être redoutés, il semble que l'on n'ait pratiquement pas ou pas du tout étudié l'insuffisance pondérale à la naissance et les problèmes ophtalmologiques, bien que certains comptes rendus anecdotiques fassent la relation entre ces problèmes et ce type de pollution. Une diminution de la fonction pulmonaire a été relevée chez des femmes népalaises ayant signalé passer beaucoup de temps auprès du poêle ainsi que chez des femmes chinoises qui utilisent des cuisinières à charbon par rapport à celles qui utilisent des cuisinières à gaz. Des symptômes de détresse respiratoire ont été associés à l'utilisation de combustibles produisant de la fumée dans l'ouest de l'Inde, au Ladakh et à l'issue de plusieurs études chinoises portant sur différents groupes d'âge, certaines auprès d'échantillons importants de population. Des cas d'infections respiratoires aigues chez les enfants, l'une des principales causes de mortalité infanto-juvénile, ont été associés à l'exposition à la fumée dans des habitations népalaises, d'après le temps passé par les enfants auprès des poêles.

Les études sur les maladies chroniques sont difficiles car il est nécessaire d'établir des antécédents d'exposition sur de longues périodes. Néanmoins, la maladie pulmonaire obstructive chronique a été associée au temps passé chaque jour auprès du poêle pour des femmes népalaises et son taux d'incidence a été jugé élevé parmi les utilisatrices de poêles à charbon comparé aux utilisatrices de poêles à gaz à Shanghai. Contrairement à ce qui avait été précédemment indiqué, la fumée dégagée par les cuisinières ne présente, semble-t-il, que peu de risque de cancer du rhino-pharynx. Toutefois, plusieurs études menées en Chine ont montré que la fumée était un facteur de risque important pour le cancer du poumon chez les femmes non-fumeuses. En outre, des cas graves de fluorose ont été observés dans plusieurs regions de Chine où les taux de fluorure dans le charbon sont élevés.

Les concentrations élevées de polluants à l'intérieur des habitations et l'importance des populations exposées (également pauvres, donc vulnérables) justifient que des ressources accrues soient consacrées à des études épidémiologiques d'échantillons importants de population en prenant les mesures de contrôle de la qualité nécessaires à l'obtention de données quantitatives fiables sur les rapports dose-réponse. Cela étant, ce que l'on sait devrait déjà suffire à inciter les ménages, les communautés et les gouvernements à redoubler d'efforts pour réduire l'exposition à ces types de pollution, par l'éducation et l'introduction de poêles améliorés, de combustibles plus propres et de meilleurs systèmes d'aération.

REFERENCES — RÉFÉRENCES

1. SAMET, J. M. ET AL. Health effects and sources of indoor air pollution. *American review of respiratory disease*, **136**: 1486-1508 (1987).
2. SMITH, K. R. Indoor air pollution and the pollution transition. In: Kasuga, M. (ed.), *Indoor air quality*. Berlin, Springer Verlag, 1990. (Supplement to the *International archives of environmental health*).
3. SMITH, K. R. Total exposure assessment: implications for developing countries. *Environment*, **30** (10): 16-20; 28-35 (1988).

2023381682

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4. SMITH, K. R. *Biofuels, air pollution and health–A global review*. New York, Plenum, 1977.

5. DE KONING, H. W. ET AL. Biomass fuel combustion and health. *Bulletin of the World Health Organization*, **63** (1): 11-26 (1985).

   DE KONING, H. W. ET AL. Combustion de biomasse et santé, **63** (2): 215-232 (1985).

6. CHEN, B. H ET AL. [Indoor air pollution due to coal combustion in China. *Modern medicine in China*], **1**: 285-289 (1989). (In Chinese).

7. DARY, O. ET AL Carbon monoxide contamination in dwellings in poor rural areas of Guatemala. *Bulletin of environmental contamination and toxicology*, **26** (1): 24-30 (1981).

8. PANDEY, M. R. ET AL. Domestic smoke pollution and respiratory function in rural Nepal. *Tokai journal of experimental and clinical medicine*, **10** (4): 471-481 (1985).

9. INDIA NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH. Comparative epidemiological studies of the effects of air pollutants. In: *Annual report, 1979*. Ahmedabad, Indian Council of Medical Research, 1979.

10. AGGARWAL, A. L. ET AL. Assessment of exposure to benzo(a)pyrene in air for various population groups in Admedabad. *Atmospheric environment*, **16** (4): 867-870 (1982).

11. PATEL, Y. S. ET AL. Indoor air pollution problems: traditional versus modern fuels. In: Berglund, B. et al. (eds), *Proceedings of the Third International Conference on Indoor Air Quality and Climate*. (Vol. 4). Stockholm, Swedish Council for Building Research, 1984.

12. KAMAT, S. R. ET AL (EDS). *Bombay air pollution – Health study*. Bombay, Municipal Corporation of Greater Bombay, 1984.

13. MALIK, S. K. Preliminary report on exposure to domestic cooking fuels and chronic bronchitis. *Indian journal of chest diseases and allied sciences*, **27** (3): 171-174 (1985).

14. PANDEY, M. R. & GHIMIRE, M. Prevalence of various types of heart disease in Kathmandu. *Journal of the Nepalese Medical Association*, **13**: 33 (1975).

15. PANDEY, M. R. ET AL. *Chronic bronchitis and cor pulmonale in Nepal*. Kathmandu, Mrigendra Medical Trust, 1988.

16. WOOLCOCK, A. J. ET AL. Studies of chronic lung diseases in New Guinea populations. *American review of respiratory disease*, **102**: 575-590 (1970).

17. BATTACHARYA, S. N. ET AL. Chronic bronchitis in rural populations. *Indian journal of chest diseases and allied sciences*, **17** (1): 1-7 (1975).

18. PADMAVATI, S. & ARORA, S. S. Sex differences in chronic *cor pulmonale* in Delhi. *British journal of diseases of the chest*, **70**: 251-259 (1976).

19. ANDERSON, H. R. Chronic lung disease in the Papua New Guinea highlands. *Thorax*, **34**: 647-653 (1979).

20. PANDEY, M. R. Prevalence of chronic bronchitis in a rural community of the hill region of Nepal; Domestic smoke pollution and chronic bronchitis in a rural community of the hill region of Nepal. *Thorax*, **39**: 331-336; 337-339 (1984).

21. ANDERSON, H. R. Respiratory abnormalities in Papua New Guinea children: the effects of locality and domestic wood-smoke pollution. *International journal of epidemiology*, **7**: 63-72 (1978).

22. KOSSOVE, D. Smoke-filled rooms and respiratory diseases in infants. *South African medical journal*, **61**: 622-624 (1982).

23. BOLEU, J. S. ET AL. Domestic air pollution from biomass burning in Kenya. *Atmospheric environment*, **23** (8): 1677-1681 (1989).

24. CAMPBELL, H. ET AL. Indoor air pollution in developing countries and acute respiratory infections in children. *Lancet*, **i**: 1012 (1989).

25. PANDEY, M. R. ET AL. Domestic smoke pollution and acute respiratory infection in a rural community of the hill region of Nepal. *Environment international*, **15**: 337-340 (1989).

26. CHEN, B. H. & WONG, J. [Effects of indoor and outdoor pollution on the immune function of schoolchildren. *Journal of environment and health*], **6** (4): 1-10 (1989). (In Chinese).

27. CHEN, B. H. ET AL. [Health stress from domestic coal combustion. *Journal of environment and health*], **4** (6): 1 (1987). (In Chinese).

28. HU, H. S. & LIU, Y. C. Evaluation of indoor air pollution and its effect on human health in Beijing's rural areas. *Environment international*, **15**: 321-335 (1989).

29. KIM, Y. S. & KREISEL, W. Effects of household exposures to carbon monoxide poisoning in Korea. In: Berglund, B. et al. (eds), *Proceedings of the Third International Conference on Indoor Air Quality and Climate*. (Vol. 4). Stockholm, Swedish Council for Building Research, 1984.

30. LU, B. Y. ET AL. [Research on human airway resistance in high and low lung-cancer prevalence regions in Xuanwei County. *Journal of environment and health*], **1** (4): 12 (1984). (In Chinese).

31. ZHOU, M. H. ET AL. [An epidemiological survey on indoor air pollution. *Journal of environment and health*], **2** (5): 20 (1985). (In Chinese).

32. ZHOU, G. D. ET AL. [An epidemiological survey on indoor pollution from various fuel combustion. In: Chen, B. H. et al. (eds), *Indoor air pollution and its health effects*]. Shanghai, Shanghai Medical University, 1987. (In Chinese).

33. KOO, L. C. ET AL. Personal exposure to nitrogen dioxide and its association with respiratory illness in Hong Kong. *American review of respiratory disease*, forthcoming.

34. XU, Z. Y. ET AL. [Air pollution and lung cancer in Liaoning Province. In: *Proceedings of air pollution and mortality*]. Beijing, Ministry of Public Health, 1984. (In Chinese).

35. DU, Y. S. ET AL. [A preliminary analysis of trends of lung cancer mortality in Guangzhou, China. *Acta academiae medicinae Guangzhou*], **12** (1): 1-22 (1984). (In Chinese).

36. OU, X. L. ET AL. [Relation between housewife lung cancer and domestic coal use. *Journal of environment and health*], **6** (1): 4 (1989). (In Chinese).

37. WANG, F. L. ET AL. [Analysis of risk factors for female lung adenocarcinoma in Herbin – Indoor air pollution. *Chinese journal of preventive medicine*], **23** (5): 270 (1989). (In Chinese).

38. YUNNAN PROVINCIAL PUBLIC HEALTH AND ANTI-EPIDEMIC STATION. [Indoor air pollution monitoring in high and low lung-cancer prevalence regions in Xuanwei County. *Journal of environment and health*], **1** (5): 14 (1984). (In Chinese).

39. HE, X. ET AL. [Lung cancer and indoor air pollution in China. In: Huang, H. (ed.), *Medicine in*

2023381683

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China: cancer, early diagnosis and control. Hong Kong, University of Hong Kong, 1986. (In Chinese).

40. MUMFORD, J. L. ET AL. Lung cancer and indoor air pollution in Xuanwei, China. *Science*, **235**: 217-235 (1987).
41. KOO, L. C. ET AL. Do cooking fuels pose a risk for lung cancer? A case control study of women in Hong Kong. *Ecology of disease*, **2** (4): 255-265 (1983).
42. KOO, L. C. Environmental tobacco smoke and lung cancer – Is it the smoke or the diet? In: Bieva, C. J. et al. (eds), *Present and future of indoor air quality*. Amsterdam, Elsevier Science Publications, 1989.
43. WEN, C. P. Nasopharyngeal cancer. In: Quinn, J. E. (ed.), *China medicine as we saw it*. Washington, D. C., Department of Health, Education and Welfare, 1974. (NIH75-684).
44. ARMSTRONG, R. W. ET AL. Self-specific environments associated with nasopharyngeal carcinoma in Selangor, Malaysia. *Social science and medicine*, **120**: 149-156 (1978).
45. CLIFFORD, P. Carcinogens in the nose and throat. *Proceedings of the Royal Society of Medicine*, **65**: 682-686 (1972).
46. HOFFMANN, D. & WYNDER, E. L. Respiratory carcinogens. In: *International symposium on identification and measurement of environmental pollutants*. Ottawa, Canadian National Research Council, 1972.
47. YU, M. C. ET AL. Epidemiology of nasopharyngeal carcinoma in Malaysia and Hong Kong. *National Cancer Institute monograph*, **69**: 203-207 (1985).
48. XIAO, Y. Y. ET AL. [Observations on dental fluorosis induced by indoor air pollution from domestic fuel combustion. *Journal of environment and health*], **4** (1): 36 (1987). (In Chinese).
49. WANG, C. L. ET AL. [An endemic fluorosis induced by domestic fuel combustion. *Journal of environment and health*], **4** (3): 12 (1986). (In Chinese).
50. YANG, D. J. [Suggestions on the diagnosis and identification of fluorosis induced by food polluted from coal combustion, using x-rays. *Chinese journal of preventive medicine*], **21** (3): 136 (1987). (In Chinese).
51. DAI, G. J. ET AL. [A survey on fluorosis induced by coal combustion. *Chinese journal of preventive medicine*], **20** (4): 217 (1986). (In Chinese).
52. ZHANG, Z. F. ET AL. Indoor air pollution of coal fumes as a risk factor of stroke, Shanghai. *American journal of public health*, **78**: 975-977 (1988).
53. PANDEY, M. R. ET AL. Indoor air pollution in developing countries and acute respiratory infection in children. *Lancet*, **i**: 427-429 (1989).

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Lung Cancer In South China

GUANGZHOU, SOUTH CHINA—After the implementation of certain processes to diminish industrial smoke and descending dusts, the quantity of SO_2 and dust in the air has decreased gradually each year here. However, the mortality rate from lung cancer is still increasing, indicating that there may be important carcinogenic factors existing aside from industrial air pollution. In response to this situation, scientists of Guangzhou Pulmonary Cancer Research Center have collected and analyzed data on the potential risk factors for lung cancer, such as population density in the city, the annual amount of tobacco sold, and the amount of coal and petroleum used.

Air pollution inside a group of 20 houses selected from four regions of the city was investigated. Air samples taken in the rooms were found to contain a higher concentration of SO_2, TSP, and particularly B(a)P than in the open air. Houses with similar types of architecture were selected for a comparative study of how air pollution is influenced by the use of coal stoves or liquified petroleum gas for cooking. Air samples from kitchens were taken during cooking and measured for concentrations of SO_2 and CO.

The tested concentrations of SO_2 and CO in the coal burning kitchens were $1.351 \pm 1.167 mg/m^3$ and 24.48 ± 21.69 mg/m^3 respectively, while those of the kitchens using liquified petroleum gas were 0.099 ± 0.103 mg/m^3 and 7.77 ± 7.84 mg/m^3. It is evident that coal burning possesses greater potential danger for air pollution.

The relative risk of lung cancer death of inhabitants with a "most often" history of contact with coal smoke was 1.71. Females living in a smoky environment here run a relative risk of lung cancer even higher than that of tobacco consumption. Because most of the house-cleaning and cooking is done by housewives in China, lung cancer among females is increasing.

Since 1956, most of the inhabitants have changed their habits of using grass and wood for fuel and instead burn bituminous coal for cooking. The small-sized stoves used are essentially without a chimney, and coal smoke floats motionless in the humid South China air. The overcrowded population in the residential areas run a stong risk of lung cancer from the contaminated air. Scientists of the Research Center are advising people to alter the construction of their stoves and to replace the use of bituminous coal for cooking with other energy sources; otherwise, lung cancer prevention activities will be less effective. □

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Meeting Report

Mutagenesis and carcinogenesis by nitropyrenes and cancer chemotherapeutics

Frederick J. de Serres * and Taijiro Matsushima

12th Joint Conference of the U.S.–Japan Panel on Environmental Mutagenesis and Carcinogenesis, U.S.–Japan Cooperative Medical Sciences Program, Shimoda, Japan, 8–10 January 1985

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The 12th Joint Conference on the Nitropyrenes and Cancer Chemotherapeutics was attended by 8 scientists from the United States where Dr. Frederick J. de Serres is Panel Chairman and 26 Scientists from Japan under the Chairmanship of Dr. Takeo Suzuki. A total of 4 sessions were held under the topics (1) Mutagenicity of Nitropyrenes, (2) Carcinogenicity of Nitropyrenes, (3) Secondary Cancer in Chemotherapy Patients and (4) Genetic Toxicology Studies in Cancer Chemotherapy.

Session I. Mutagenicity of Nitropyrenes

Dr. Yoshinari Ohnishi, The University of Tokushima, Tokushima, reported on the measurement of the mutagenicity of complex environmental mixtures and foods and the determination of the amounts of nitropyrenes in them. Nitropyrenes were found in the neutral and acidic fractions of exhaust particles from a diesel truck, in the benzene–ethanol (4 : 1) extract from the particulate fraction collected on Teflon-coated filters from a radiant kerosene heater and in the neutral fraction of sauce-coated, grilled chicken. The mutagenicity of these fractions was assayed with Salmonella strain TA98 in the absence of S9 mix. Furthermore, the carcinogenicity was examined by injecting 150 μg of 1,6-dinitropyrene mixed with bees wax and tricaprylin as a pellet into the lungs of F344 rats. The incidence of lung carcinomas was 23 out of 28 rats at week 72. In addition using germ-free and conventional rats, the metabolism of tritium labelled 1-nitropyrene was studied. The mutagenic activity of the feces and urine was studied using TA98 both with and without S9 mix and metabolites were identified using reversed phase HPLC after treatment with β-glucuronidase and their identity was confirmed by coelution with reference standards, by their UV spectra and by their mass spectra. These results suggest that the intestinal microflora reduces nitropyrenes to amino derivatives and that hydroxylation, conjugation and probably *N*-acetylation occur in the liver.

Dr. Robert Mermelstein, Xerox Corporation, Rochester, NY, reported on the extensive research on the genetic toxicology of nitrated pyrenes resulting from the discovery of potent bacterial mutagenicity and their widespread low-level dissemination. Nitropyrenes are potent, direct-acting mutagens for Salmonella and the pattern of activity indicates that frameshift mutations are being induced. The potency of individual nitropyrenes also differs as a function of tester strain. For example, 1,3-dinitropyrene and 1,3,6-trinitropyrene display the highest mutagenicity in Salmonella strain TA1538, 1,8-dinitropyrene is most active in strain TA98. There is substantial evidence for the mutagenicity of nitropyrenes in cultured mammalian cells: Chinese hamster ovary fibroblasts, Chinese hamster lung fibroblasts, hu-

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man hepatoma derived cell line Hep G-2 and human diploid lymphoblasts; however they are inactive in a human XP cell line. Various nitropyrenes have also been shown to stimulate DNA repair synthesis in HeLa cells, in primary rat hepatocytes as well as in Hep G-2 cells. Both 1-nitropyrene and 1,8-dinitropyrene have been shown to induce chromosome aberrations. Nitropyrenes exhibit a wide spectrum of genotoxic effects which are evident in both microbial and mammalian systems. The nature and extent of such activity depend on the metabolic capability of the individual test systems.

Dr. Hiroshi Tokiwa, Fukuoka Environmental Research Center, Dazaifu, discussed various sources of nitropyrenes in the environment and speculated that the increased use of radiant kerosene heaters and gas and liquified petroleum gas burners since 1955 may have been responsible for a concomitant increase in lung cancer in Japan. The emission soot from such burners contains mutagenic activity caused by dinitropyrenes and nitrofluoranthenes. When the gaseous fuel was burned under conditions of incomplete combustion, some polycyclic aromatic hydrocarbons (PAH) were found in addition to the nitropyrenes. In these combustion products of fuels, the quantities of 1-nitropyrene were unexpectedly low in contrast with those found in diesel emission.

Dr. Minako Naguo, National Cancer Center Research Institute, Tokyo, reported on the relative mutagenicity of 1,8-dinitropyrene (1,8-DNP) in Salmonella and in Chinese hamster lung cells in culture. In Salmonella, 1,8-DNP gives 9.4×10^4 revertants/μg with strain TA98 and 1.2×10^5 revertants/μg with strain TA100, but only 5.2×10^{-2} diphtheria toxin resistant mutants per 10 survivors/μg (−S9 mix).

Oncogenes of 8 fibrosarcomas induced by subcutaneous injection of 40 mg of 1,8-DNP were examined using NIH 3T3 cell transfection assay and Southern blot analysis. 4 tumors induced transformed foci in NIH 3T3 cells by DNA-mediated gene transfer. One primary transformant and its 7 secondary transformants contained active rat c-K-*ras*. The transforming gene of 6 other primary transformants obtained from 3 tumors were not *ras* family or *neu* genes.

Dr. Herbert S. Rosenkranz, Case Western Reserve University, Cleveland, OH, discussed the need to be able to predict the activity of, as yet, untested nitroarenes in the environment based on the properties of those nitroarenes whose properties have already been studied. Two different approaches are being used: (1) Electrochemical reduction of nitroarenes and (2) Computer Automated Structure Evaluation (CASE) Methodology. Electrochemical reduction can be used as an indication of the ease of reduction of the nitro function of the nitroarenes. A relationship was found between the ease of nitro-reduction ($E1/2$, the voltage of the half-wave potential) and the mutagenicity of these compounds in Salmonella assay using strains TA98 and TA1538. The $E1/2$ values were used to calculate the energy of the lowest unoccupied molecular orbital (LUMO energy) and this established that the mutagenicity of nitroarenes is directly related to LUMO. Since LUMO energies can be directly calculated, it is feasible to predict the mutagenicity of untested nitroarenes on the basis of the calculated LUMO energies. Using the CASE method, a mechanism has been developed for predicting the activity of untested nitroarenes based upon the presence of certain automatically determined structures. This CASE system has identified two activating and two deactivating substructures which explain the mutagenicity of nitroarenes. This method can also be used to investigate whether the functionalities responsible for mutagenicity and carcinogenicity are indeed identical.

Session II. Carcinogenicity of Nitropyrenes

Dr. Charles M. King, Michigan Cancer Foundation, Detroit, MI, reported on that induction of rat mammary gland tumors with various nitropyrenes. The initial evaluation of the carcinogenic potential of 1-nitropyrene employed both male and female CD rats. Treatment by subcutaneous injection was given from birth through approximately 60 days of age to provide exposure adequate for the development of either liver or mammary tumors. Tumor formation at the suprascapular site of injection was observed in both sexes at approximately the same frequency. Malignant mammary tumor induction was observed in a dose-dependent fash-

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ion in the females. No evidence of liver tumor formation was detected. The results of this initial study was published in Cancer Res., 44 (1984) 1158–1162. In a second experiment, 1-nitropyrene, 2-nitropyrene, 4-nitropyrene, 1-acetylaminopyrene, *N*-hydroxy-1-acetylaminopyrene, *N*-hydroxy-2-acetylaminofluorene or DMSO alone were administered intraperitoneally to 30-day-old female rats. Mammory tumor induction was observed only with the 4-nitropyrene and *N*-hydroxy-2-acetylaminofluorene. Evidence of neoplastic nodule formation in the liver was observed only with the 3 acetylated derivatives.

Dr. Hiroko Ohgaki, National Cancer Center Research Institute, Tokyo, reported on experiments with highly purified samples of 1-nitropyrene (NP) and the 1,3-, 1,6- and 1,8-dinitropyrenes (DNP) to evaluate their carcinogenicity after subcutaneous injection in F344 rats. Test chemicals dissolved in 0.2 ml DMSO were injected twice a week for 10 weeks. The three dinitropyrenes were found to produce subcutaneous tumors at the site of injection in 10/10 rats injected with a total of 4 mg of the test chemical.

Dose-response relations were studied by injecting F344 rats subcutaneously with 4, 0.4 or 0.04 mg of 1,8-DNP. Sarcomas at the site of injection were found in 10/10 animals by 127 days, 10/10 animals by 156 days 9/10 animals by 320 days, respectively, for each of the three treatments. Previous studies with 1-nitropyrene (Cancer Lett., 15 (1982) 1) showed that it produced subcutaneous tumors at the site of injection in 8/17 rats between 162 and 319 days. However, this batch of 1-nitropyrene was later found to be contaminated with 0.2% 1,3-DNP, 0.3% 1,6-DNP and 0.3% 1,8-DNP raising the possibility that the carcinogenicity was due to the dinitropyrene contaminants. The 1-NP experiment was repeated using a highly purified sample where the DNP level was < 0.05%, 1,3,6-trinitropyrene < 0.05% and 1,3,6,8-tetranitropyrene < 0.05%. 10 and 20 male F344 rats were each injected subcutaneously 2 times for 10 weeks to give a total dose of 4 or 40 mg 1-NP. No tumors were found by day 650 clearly demonstrating that the previous positive carcinogenicity test with 1-NP was due to the trace levels of DNP contaminants.

Dr. Shozo Takayama, National Cancer Center Research Institute, Tokyo (paper presented in his absence by Dr. Shigeaki Sato) reported on recent experiments to study the induction of lung cancer by 1,6-dinitropyrene. The 1,6-DNP was ground and suspended at a concentration of 2.5 mg/ml and a long needle was used to give a tracheal dose of 0.5 mg once a week for 26 weeks into 10-week-old female (10) and male (10) Syrian golden hamsters. All treated, and a similar number of saline-treated control animals, were observed for 48 weeks after the first treatment. Lung tumors started to appear in the female 1,6-DNP-treated animals after 20 weeks and many additional tumors appeared during the next 20 weeks in both male and female animals. Lung adenocarcinomas were found in 10/10 males and 9/10 females, and myeloid leukemias were also induced in 6/10 males and 6/10 females. No tumors were found in the control animals.

Dr. Hiroshi Tokiwa, Fukuoka Environmental Research Center, Dazaifu, reported briefly on some experiments to evaluate the carcinogenic activity of a sample of 99.9% pure 1,6-DNP in BALB/c mice. Using total doses of 2 mg given subcutaneously with 0.1 mg/week for 20 weeks a comparison was made between pure 1-NP and 1,6-DNP. No tumors were found with 1-NP, malignant fibrous histocytomas at the site of injection were found with 1,6-DNP and the incidence of lung tumors did not differ significantly from that found in the control animals in either treated group. Similar tumors in the 1,8-DNP-treated mice were found at the high rate when 1 mg of 1,8-DNP was inoculated subcutaneously.

Dr. Kazuro Iwai, Japan Anti-tuberculosis Association, Tokyo, reported on chronic inhalation experiments to investigate the tumorgenicity of diesel exhaust particles in F344SPF rats. Proliferative changes of bronchiolar and alveolar epitheliums were found in the early stage and both benign and malignant lung tumors were induced in the late stage.

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Session III. Secondary Cancer in Chemotherapy Patients

Dr. Shaw Watanabe, National Cancer Center Research Institute, Tokyo, reported on his studies on second primary malignancies in long-term survivors of cancer chemotherapy. Patients who received alkylating agent therapy for cancer of the ovary, breast, lung, brain and myeloma have also been shown to be at increased risk for developing acute leukemias. Data collected by Fujimoto in Osaka on 31 cases with secondary heterochronous leukemia were analyzed by matched case-control study. The cases with leukemias revealed a high occurrence of leukemias in chemotherapy and radiation and less in the surgery only group. In a hospital based study performed at the National Cancer Center, 270 multiple primary cancer (MPC) were found among 9191 patients initially treated for GI tract cancer, 94 MPC among 1967 initial lung cancer patients, 62 MPC among 2715 initial breast cancer patiens and 68 MPC among 2682 initial uterine cervical cancer.

Dr. Leslie L. Robison, University of Minnesota Health Sciences Center, Minneapolis, MN, discussed the occurrence of secondary tumors in the survivors of childhood cancer. During the past 20 years significant advances have been made in the treatment of childhood malignancies. Approximate 5-year survival rates are: acute lymphoblastic leukemia (65%), acute nonlymphoblastic leukemia (40%), brain tumors (40%), Wilms' tumor (90%), Hodgkin lymphoma (90%), neuroblastoma (30%) and retinoblastoma (85%). Second malignant neoplasms (SMN) represent one of the most serious complications for survivors of childhood cancer. The incidence of SMN in persons with cancer in childhood has been estimated to be between 10–15% at 25 years following the diagnosis of the initial malignancy. Most frequently reported SMN were in patients with first tumors of retinoblastoma (18%), Hodgkin disease (14%), soft tissue sarcomas (14%), Wilms' tumor (12%) brain tumors (11%), neuroblastoma (10%), bone sarcomas (6%), and leukemia or non-Hodgkin lymphoma (8%). Studies conducted by the Late Effects Study Group in conjunction with the National Cancer Institute have assessed the risk of SMN associated with specific groups of chemotherapeutic agents. After adjusting for radiation exposure, alkylating agents were found to be significantly associated with an increased risk for leukemia. A significant dose response was identified with highest levels of alkylating agent exposure denoting a 23-fold increased risk for leukemia. In addition, a 2-fold risk for bone cancer as a second malignancy was found for alkylating agent exposure independent of radiation exposure. Well-designed studies of large cohorts of children diagnosed and treated for cancer will be needed to accurately assess the risk of SMN and to provide insight into the genetic and treatment components of the development of SMN.

Session IV. Genetic Toxicity Studies in Cancer Chemotherapy

Dr. John Mulvihill, National Cancer Institute, Bethesda, MD, reported on studies of cancer and genetic disease in progeny of cancer patients. Cancer treatment is often designed to interact specifically with DNA and to block its function. Cancer therapy can cause somatic cell mutation, as evidenced by the excessive risk of additional primary malignant neoplasms and other measures of genetic damage including chromosome abérrations. Cancer and its treatment may also cause infertility. If a pregnancy is established in or by a cancer patient, the outcome is of interest: pregnancies occurring *before* cancer diagnosis serve as a control experience and a measure of the heritable predisposition to cancer (or to other genetic diseases). Pregnancy occurring *during* cancer therapy can be evaluated for teratogenicity and embryotoxicity. Pregnancies *after* cancer therapy reflect survival of gonads and intact reproductive tracts as well as potential germ cell mutagenicity. In 9 large studies with over 467 patients and 993 complete pregnancies, only 32 (4%) of 747 live-borns had one or more major birth defects, a rate comparable to that found in the general population. None was a classical sentinel phenotype. A new study of survivors of childhood cancer focused on the occurrence of new primary cancers, late morbidity, and infertility in the cases, and cancer and birth defects in their offspring. Patients were studied for secondary malignancies among those

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children who had cancer under the age of 20 between 1945 and 1974, and who had survived at least five years and reached the age of 21 years. 97 subsequent tumors occurred in 2293 cancer cases. 8 of 2328 offspring of cases had cancer and 10 of 4789 offspring of controls. One or more major birth defects occurred in 192 (8%) of case children and 353 (7.4%) of control children. These rates are not statistically different.

Dr. Michael D. Shelby, National Institute of Environmental Health Sciences, Research Triangle Park, NC, reported on studies to determine the frequencies of chromosome aberrations and sister-chromatid exchange in control populations. The measurement of chromosomal damage in peripheral lymphocytes offers a practical means of detecting exposure of humans to genotoxic agents. Comparisons of results obtained with different groups of exposed individuals is often difficult due to differences in protocols. Thus, agreement on a basic protocol for human cytogenetic studies is needed, as is information on the background frequencies of chromosomal aberrations (CA), particularly chromatid-type aberrations, and sister-chromatid exchanges (SCE), their variability and the sources of variability. Such information cannot take the place of concurrent controls but will be useful in the design and interpretation of future cytogenetic studies of populations exposed to potential chromosome-damaging agents. In work carried out at the Oak Ridge National Laboratory and at the Brookhaven National Laboratory under NIEHS/NTP contract, CA and SCE data have been obtained on 357 subjects not known to be exposed to clastogenic agents, the majority selected using a stratified, random sampling scheme. In comparisons of chromosome aberration data using the dichotomous variables: sex, smoking, work with solvents, work with radiation and use of prescription drugs, no significant differences were seen. SCE frequencies, which average 8.49 per cell with a range of 5.70–14.98, were significantly higher in smokers than in non-smokers. Preliminary analyses have not shown the other variables to influence SCE frequencies.

Dr. Yutaka Ishii, Osaka University, Osaka, reported on his studies to evaluate the genetic effects of various chemotherapeutic agents by measuring Sister-Chromatid Exchange (SCE) frequencies in peripheral blood lymphocytes from cancer patients. The agents studied were mitomycin C (MC) and cyclophosphamide (CP). In the MC experiments the drug was injected intraveneously twice a week for 2 weeks in 2 patients with gastric cancer. After the first and second treatment with MC, SCE frequency increased with time, reached a peak after 24 h, and then declined returning to the pretreatment level at about 2 days following treatment. After the third and fourth course of injections, SCE frequency increased further and did not return to the pretreatment level by 3 days after treatment. However SCE frequencies were at pretreatment levels by 3 months after treatment. A similar experiment was performed with CP. After injection of the drug SCE frequencies would increase rapidly with time, reaching a peak in 24 h and returning to pretreatment levels on the 7th day. Similar cycles of rapid increase and slow decrease in SCE frequency were obtained after each of the subsequent 5 injections, resulting in a gradual rise in the basal and the maximum level of SCE. In the 5th month after termination of therapy, SCE frequency returned to the pretreatment level. Thus, SCE frequency may quantitatively reflect the degree of genomic damage by a chemotherapeutic agent at the time of administration but it may not be a good index of genomic damage persisting for a long time after therapy.

Dr. Mortimer Mendelsohn, Lawrence Livermore National Laboratory, Livermore, reported on newly developing assays as LLNL to measure somatic and germinal genetic damage in the human. The first project involves the development of an assay for gene loss in human red blood cells. Highly specific fluorescent monoclonal antibodies against the products of the M and N alleles of glycophorin A have been developed and can be differentially measured (red fluorescence for the N allele and green fluorescence for the M allele) on the red cell surface by flow cytometry. MN individuals constitute about 50% of the human population. The two alleles act independently so if one or another is inactivated the glycophorin A made is produced only by the active allele. Experiments are in progress to measure the changes in frequency

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in the red blood cells from cancer chemotherapy patients. In another line of work hemoglobin assays for mutations resulting in single amino acid changes in human, monkey and mouse red blood cells are in progress. The previously available polyclonal immunological assay for human hemoglobin S is now supplanted by a monoclonal approach and is supplemented by a variety of other antibodies which also recognize the effects in the hemoglobins of several species of single-base changes in the DNA of precursor cells. New work has been started to develop a monoclonal antibody against protamines (histone-like proteins in the sperm) made in the late stages of spermatogenesis. The protamines have been sequenced to determine their normal amino acid composition, but there still is a question as to whether mutations that would alter this sequence would be compatible with normal spermatogenesis. In another project antibodies to bromodeoxyuridine (BrDR) permit testing of the effect of the BuDR on the production of sister-chromatid exchanges (SCE) at very low doses. These studies have shown that BuDR does cause SCE, but at very low levels a plateau is reached which may reflect the normal spontaneous SCE frequency. New experiments with flow-cytogenetic methods for karyotyping have been used in studies with the Chinese hamster. By measuring the DNA fluorescence for chromosomes at metaphase all chromosomes can be characterized. Similar studies have been done with human chromosomes using the Hoechst stain or the chromomycin A stain. Different chromosomes map in a characteristic place. When fluorescence is mapped against DNA content; chromosomes 9-12 form a single elipse and chromosomes 14 and 15 overlap but all other chromosomes are separate from one another. Flow karyotyping can now be used to determine whether the karotype is normal or abnormal and can be used in combination with amniocentesis for prenatal diagnosis. This same technology can be used to get a profile of DNA along the length of chromosomes and thus to identify centromere location and dicentrics. The sorting of human chromosomes leads to the construction of gene libraries of specific chromosomes. A total of about 4×10^6 chromosomes of a particular chromosome in the genome can be obtained with this methodology and the DNA extracted. In a joint project with the Los Alamos National Laboratory, half of the human genome has now been cloned, chromosome by chromosome. In other lines of work recombinant DNA markers for individual human chromosomes are being developed. By using fluorescent markers these chromosome specific DNA probes can be used to stain interphase cells to study the spatial array of the DNA in individual chromosomes during this stage of the cell cycle that has been refractory to conventional methods of cytological analysis. The final project involves study of the cytogenetics of mature human sperm. This work is possible because the hamster oocyte will accept human sperm. When colchicine is used to arrest cell division in the early stages of development of the fertilized egg, the haploid human sperm set of chromosomes can be analyzed and karyotyped. A total of 2468 karyotypes have been studied; 181 (7.5%) have structural abnormalities; 21 (0.9%) are hyperploid and 29 (1.6%) are hypoploid. The abnormality rates for individuals donors seem to be stable with time suggesting that this assay provides a true measure of genetic damage. However, sperm karyotypes consistently yielded higher aberration frequencies in the same individual than is obtained with lymphocytes in culture; the basis for this difference has not as yet been determined. This technique does provide a mechanism to evaluate the genetic effects of exposure to mutagenic/carcinogenic agents and would be especially useful in those cases where a karyotype analysis has been made prior to such exposure so that each individual can serve as his own control.

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ON THE RELATIONSHIP BETWEEN SMOKING AND FEMALE LUNG CANCER

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There is still controversy about the relationship between cigarette smoking and female lung cancer. The mortality rate of female lung cancer in Tianjin is the highest in China ($28.3/10^5$). The female smoking rate in Tianjin is also the highest in China. Therefore we had conducted a case-control study of female lung cancer to illustrate it.

MATERIAL AND METHODS

We conducted a 1:1 pair matched case-control study.

1. Cases: 157 female lung cancer cases all resident in Tianjin more than 10 years. Squamous cell carcinoma 35(22.3%); Small cell carcinoma 31(19.7%); Adenocarcinoma 58(36.9%); Large cell carcinoma 4(2.5%); Cell type unknown 29(18.5%). Cases were diagnosed: 133(84.7%) histologically or cytologically; 17(10.8%) by CT; 7(4.5%) clinically or by X-ray.

2. Controls: 157, matched with sex, race, age(±2 years) and marital status.

RESULTS

1. The case group is a quite representative of the Tianjin female lung cancer. The age group structure and distribution of residents of the lung cancer group is quite similar with those of 1983 Tianjin female lung cancer. Smoking rate of the control group(40.8%) is quite similar with that of the Tianjin adult female population(39.5% &58%).

2. The age, education, occupation, race, marital status, birth place, resident place of the case and control groups have no significant difference($P>0.05$).

3. Female lung cancer and active smoking

OR of active smoking is 3.05, PAR% is 57.4% (Table 1).

TABLE 1. OR OF SMOKING

		Controls	
		Smoker	Nonsmoker
Cases	Smoker	45	58
	Non-smoker	19	35

OR=3.05, 95%CI=1.77-5.30
Adjusted OR=2.6, 95% CI=1.4-4.6, $P<0.001$

Exposure rate of cases:

$$\frac{45+58}{157}=65.6\%$$

$$PAR\%=\frac{.656(3.05-1)}{.656(3.05-1)+1}=57.4\%$$

There is quite obvious dose-effect relationship between lung cancer risk and number of cigarettes smoked per day and year of smoking(Table 2).

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OR is higher of those smoking deeper than those smoke superficially or non-smoking (Table 3). OR is higher among those start smoking earlier (Table 4).

TABLE 2. LUNG CANCER RISK AND NO. OF CIGARETTES AND YEAR OF SMOKING

No. of cigarettes/day	OR	95% CI of OR
0-	1	
1-	1.81	1.40-2.33
11-	3.27	2.28-4.68
21-	5.90	3.79-9.18
Year of smoking		
0	1	
1-	1.73	1.38-2.18
20-	3.00	2.17-4.16
40-	5.20	3.49-7.75

TABLE 3. OR AND DEGREE OF INHALATION (M-H METHOD)

	No	Occasional	Deep
Case	54	37	66
Control	98	33	26
OR	1	2.03	4.61

P<0.01

TABLE 4. OR AND AGE ONSET OF SMOKING (M-H METHOD)

Age	Group	Non-smoking	21	16-20	15	P
<44	Case	8	1	3	0	>0.05
	Control	12	0	1	0	
45-	Case	16	8	17	14	<0.01
	Control	29	9	14	3	
55-	Case	24	13	13	15	<0.01
	Control	35	18	6	5	
65-	Case	6	6	6	7	<0.01
	Control	17	4	2	2	
	OR	1	1.59	3.10	6.3	<0.01

4. Female lung cancer and passive smoking.

We had calculated the OR of passive smoking from husband, father, mother and colleagues, only that from husband is quite significant.

The non-smoking female cases and controls with smoking or non-smoking husband is as table 5. The OR is 2.16 (P<0.05).

TABLE 5. OR OF SMOKING HUSBAND TO NON-SMOKING WIFE

	Husband	
	Smoker	Non-smoker
Case	34	20
Control	41	52

OR=2.16, 95% CI=1.01-4.53,

P<0.05

Exposure rate of cases

$$= \frac{34}{34+20} = 0.63$$

$$PAR\% = \frac{.63(2.16-1)}{.63(2.16-1)+1} = 42.2\%$$

OR of female lung cancer increases with the number of cigarettes smoked per day by her hus-

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band and the duration of exposure to her husband's smoking(Table 6).

5.OR of either active or passive and combination of active and passive smoking is as table 7.

TABLE 6.OR OF FEMALE LUNG CANCER OF SMOKING HUSBAND

HUSBAND SMOKING	OR	95%CI OF OR
CIGARETTE PER DAY		
0	1	
1-	1.40	1.12-1.76
10-	1.97	1.42-2.72
20-	2.76	1.85-4.10
YEARS OF EXPOSURE		
0	1	
1-	1.49	1.15-1.94
20-	2.23	1.54-3.22
40-	3.32	2.11-5.22

TABLE 7.OR OF ACTIVE AND PASSIVE SMOKING FROM HUSBAND

		ACTIVE SMOKING(WIVES)	
		NO	YES
HUSBAND SMOKING	NO	1.0	2.61(1.4-4.6)
	YES	1.86(1.04-3.5)	4.90(1.8-9.5)

If a smoking woman with smoking husband,the OR of lung cancer is 4.9,exposure rate is 81% (83/103).

$$PAR\% = \frac{.81\ (4.9 - 1)}{.81(4.9-1) + 1} = 75.95\%.$$

A non-smoking woman with smoking husband,the OR of lung cancer is 1.86,exposure rate is 63% (34/54).

$$PAR\% = \frac{.63\ (1.86 - 1)}{.63(1.86-1) + 1} = 35.1\%.$$

According to 103 smoking female lung cancer cases about 78.23(103 X .7595) are due to smoking,while the 54 non-smoking female lung cancer cases about 18.95(54 X .351) are due to passive smoking from her husband.

That is $\frac{78.23+18.95}{103+54} = 61.9\%$ of female lung cancer in Tianjin may attribute to active smoking and passive smoking from their husbands.

6. OR of female lung cancer due to other causes.

Occupational exposure: Textile workers,workers expose to asbestos, benzene,etc. OR=3.1,95% CI=1.58-6.02.

OR of history of lung diseases (include pulmonary TBC,chronic bronchitis,pulmonary infection,etc.)is 2.64.Adjusted with conditional regression model,OR=2.12,95%CI of OR=1.23-3.63.

OR of lung cancer and cooking with coal is shown in table 8.

7. Joint Effect of the Risk Factors.

Multifactor analysis by conditional regression method demonstrate that the combination of active smoking,passive smoking from husbands, occupational exposure,history of lung diseases and 4×10^4 hours cooking with coal makes the OR being about 50 in comparison with those

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without the above risk factors and cooking with coal less than $3X10^4$ hours. 95% CI of OR=13.7-185.3.

TABLE 8. OR OF LUNG CANCER AND COOKING WITH COAL

DURATION OF COOKING(hrs)	OR	95% CI of OR
$1X10^4$(1.5 hr/day,20 yrs)	1.54	1.20-1.96
$2X10^4$(1.5 hr/day,40 yrs)	2.36	1.66-3.34
$3X10^4$(2 hrs/day,42 yrs)	3.62	2.36-5.55
$4X10^4$(3 hrs/day,37 yrs)	5.56	3.40-9.10

CONCLUSION

1. Both active smoking and passive smoking from her husband are the most important risk factors of female lung cancer in Tianjin. About 60% of female lung cancer in Tianjin may be attributed to smoking.

2. There is joint effect of smoking with occupational exposure,history of lung diseases and cooking with coal.

REFERENCES

1. Hirayama T (1981) Brit Med J 282:183

2. Xu RH,Geng GY (1983) Chinese J Epidemiol 4:193-197

3. Geng GY (1980) In: Geng GY (eds) Epidemiology.People's Medical Publishing House,Beijing, vol I, pp 153-158,188-191

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Lung Cancer and Indoor Air Pollution in Xuan Wei, China

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In Xuan Wei County, Yunnan Province, lung cancer mortality is among China's highest and, especially in females, is more closely associated with indoor burning of "smoky" coal, as opposed to wood or "smokeless" coal, than with tobacco smoking. Indoor air samples were collected during the burning of all three fuels. In contrast to wood and smokeless coal emissions, smoky coal emission has high concentrations of submicron particles containing mutagenic organics, especially in aromatic and polar fractions. These studies suggested an etiologic link between domestic smoky coal burning and lung cancer in Xuan Wei.

XUAN WEI COUNTY, IN YUNNAN Province, China, has a population of about 1 million people, more than 90% of whom are farmers. Local industries include coal mining, electric power generation, and light manufacturing. The county has 20 communes with populations of 30,000 to 60,000. Tobacco smoking is common in males (40% or more), but rare in females (less than 0.1%). Local residents have traditionally used one of three major fuel types—"smoky" coal, "smokeless" coal, or wood—for domestic cooking and heating. The distribution of mines supplying smoky and smokeless coal is shown in Fig. 1. Fuel burning in shallow unvented pits has resulted in high indoor air pollution levels. Women customarily start the fire and cook; men generally spend most daylight hours outside the home.

The local medical care system of barefoot doctors, clinics, and hospitals ensures thorough lung cancer detection throughout the county. (In this report, "lung cancer" encompasses carcinomas of lung parenchyma, bronchus, and trachea.) Age-adjusted and unadjusted lung cancer mortality rates in China, Yunnan Province, and Xuan Wei are shown in Table 1 (*1*). Annual age-adjusted rates in Xuan Wei from 1973 to 1979 were 27.7 in males, among China's highest, and 25.3 in females, China's highest (*2*). The similarity between male and female lung cancer rates was unusual. In Xuan Wei, lung cancer was the only surveyed cancer for which mortality exceeded the national average (*1*). In the late 1970's, a clinical survey was also conducted to confirm the high lung cancer rates in Xuan Wei. In a surveyed population of 91,187 people, 262 lung cancer cases (287/100,000) were detected. Within this population, detection rates in farmers, office workers, and coal miners were 339, 118, and 15 per 100,000, respectively. This observation suggests that Xuan Wei lung cancer is not associated with nonagricultural occupations.

Fig. 1. Map of Xuan Wei County, showing commune boundaries, each commune's unadjusted annual lung cancer mortality rate per 100,000 (both sexes, 1973–75), and mines supplying domestic coal: (●) smoky coal and (○) smokeless coal. Designated communes: CG, Cheng Guan; LB, Lai Bin; PL, Pu Li; RS, Re Shui; RC, Rong Cheng; and YL, Yang Liu.

Unadjusted annual lung cancer mortality rates vary greatly across Xuan Wei communes (Fig. 1). Rates are generally highest in the central communes, especially Cheng Guan (CG), Lai Bin (LB), and Rong Cheng (RC), where smoky coal from LB is burned in more than 80% of homes. Between 1973 and 1975, the average of mortalities in communes with smoky coal mines (including RC and CG) was 34.7 per 100,000, as compared to 4.1 in communes without smoky coal mines. In 1982, a survey of past fuel use was conducted in more than 90% of homes in 11 Xuan Wei communes. As shown in Table 2, the commune-specific lung cancer mortality (1973–1975) was highly related to the commune-specific percentage of homes using smoky coal before 1958.

Thus, lung cancer mortality in Xuan Wei is associated with the domestic use of smoky coal. This association is especially strong in women, since they rarely use tobacco. At the same time, the wide variation in mortality across communes with smoky coal mines leaves open the possibility that specific environmental determinants of lung cancer may be more geographically restricted than is the broad entity "smoky coal."

To evaluate further the relation between domestic fuel and lung cancer in Xuan Wei, indoor air was characterized in CG and LB communes, where mortality is high and smoky coal is the predominant fuel, and in Re Shui (RS) commune, where mortality is low and wood (67%) and smokeless coal (33%) are the fuels used (Fig. 1). In each commune, indoor air was sampled in the fall of 1983 in four homes (typical in size, structure, and fuel burning for each commune) during fuel burning. Lung cancer had occurred in one each of the CG and LB homes. Smoky coal was burned in all sampled CG and LB homes; wood was burned in all sampled RS homes. Because of logistic difficulty of sampling RS homes in which smokeless coal was used, smokeless coal was transported from RS and burned in one CG home. In the spring of 1984, four homes in RS burning smokeless coal routinely were sampled to confirm the previous study. High-volume (HV) samplers (flow rate 1.2 m^3/min), with size-selective inlets (SSI), collected particulate matter smaller than 10 μm in diameter (PM10) on filters. Samplers were located 1.5 m from the fire and operated during three daily cooking periods (two cooking periods in LB) for 2 days, averaging 4 hours per day. At one CG home, a medium-volume (MV) sampler (flow rate 0.11

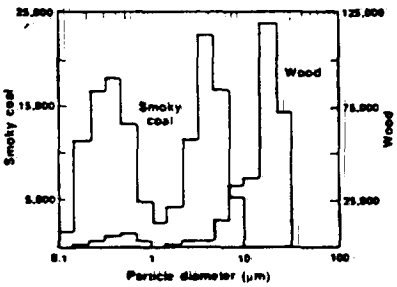

Fig. 2. Particle size distributions of indoor air particles collected during the combustion of smoky coal and wood. The y axis represents the particle volume (in cubic micrometers) within specified particle diameter range.

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Table 1. Annual lung cancer mortality rates in China and the United States.

Place	Time period	Mortality rate (per 100,000)						
		Unadjusted			Age-adjusted to 1964 China population		Age-adjusted to 1970 U.S. population	
		Males	Females	Combined	Males	Females	Males	Females
China	1973–75			5.0	6.8	3.2	12.3	5.7
United States	1970	53.7	12.0		30.0	6.3	53.7	12.0
Yunnan Province	1973–75			2.8	4.3	1.5	6.9	2.5
Xuan Wei County	1973–79	27.0	24.5		27.7	25.3	43.2	38.7
Three high-mortality Xuan Wei communes (Cheng Guan, Lai Bin, Rong Cheng)	1973–79	114.4	120.6		118.0	125.6	186.8	193.4
55- to 59-year age group in three high-mortality communes	1973–79	849.4	904.0					
Three low-mortality Xuan Wei communes (Pu Li, Re Shui, Yang Liu)	1973–79	4.0	2.8		4.3	3.1	5.8	4.3

m^3/min) with a PM10 SSI, a filter, and an XAD-2 resin trap collected particles and semivolatile organics. Each of the three fuel types was burned 6 hours per day for 2 days. During smoky coal and wood burning, a personal sampler (flow rate 1 liter/min) collected particles for physical characterization, including sizing by scanning-electron microscopy and elemental analysis by x-ray fluorescence analysis. The fuel samples of smoky and smokeless coal from mines in LB and RS, respectively, were analyzed according to the methods of the American Society for Testing and Materials (ASTM) (*3*).

Organic material was removed from the filters by Soxhlet extraction and XAD-2 with dichloromethane. The filter extracts were then fractionated into aliphatics, aromatics, moderately polar, and polar components by silica gel fractionation (*4*). Extracts and fractions were analyzed with a Finnigan 4500 gas chromatography/mass spectrometry (GC/MS) (*5*). With the MS in the multiple ion detection mode, the extracts were quantitatively analyzed for 26 compounds, including the polycyclic aromatic hydrocarbons (PAH) and nitrogen heterocyclics that have shown animal carcinogenicity (*6*). To identify major components, the extracts were further analyzed with the MS in the full-scan detection mode. The standard *Salmonella typhimurium* plate incorporation assay with minor modifications was used to assess the mutagenicity of the organic extracts and fractions (*7, 8*). Samples were tested in strain T98 with and without metabolic activation by S9. The fractions showing the most mutagenicity were further analyzed with the MS in the full-scan detection mode.

The smoky coal contained 23.1% volatiles, 66.7% carbon, 23.5% ash, and 0.2% sulfur; its heating value was 27.1 MJ/kg. By ASTM classification (*3*), the smoky coal was ranked as a medium-volatile bituminous coal with low sulfur and high ash. Except for elevated levels of nickel (64 ppm), its trace elemental concentrations were comparable to those of analyzed U.S. anthracite and bituminous coals. The smokeless coal contained 13.8% volatiles, 38.5% carbon, 1.9% sulfur, and an extremely high level of ash, 49.3%; its heating value was low, 14.5 MJ/kg.

The concentrations of airborne particles (PM10) inside homes during smoky coal and wood combustion were very high [that is, 24.4 ± 3.3 (mean ± SEM), 9.5 ± 1.6, and 22.3 ± 2.0 mg/m^3 for CG, LB, and RS, respectively], whereas concentrations during combustion of smokeless coal were considerably lower [1.8 mg/m^3 for the CG home burning smokeless coal (1983) and 1.1 ± 0.1 mg for the four RS homes burning smokeless coal (1984)]. Figure 2 shows the size distributions of indoor air particles during combustion of smoky coal and wood. Both distributions were bimodal. Fifty-one percent of the particles from smoky coal combustion were less than 1 μm in diameter; the rest were between 1 and 10 μm. Most particles were spherical. In marked contrast, 94% of the particles from wood combustion ranged from 1 to 30 μm; only 6% were less than 1 μm in diameter. The x-ray fluorescence analysis showed that most of the particles collected during smoky coal combustion were not inorganic. This was confirmed by the solvent extraction studies, which showed a high percentage of organic mass in the particles from smoky coal combustion. The ratio of organics to soot to unburned fuel in the particles from smoky coal, smokeless coal, and wood combustion were 80:10:10, 10:30:60, and 10:40:50, respectively.

The samples from smoky coal combustion contained high concentrations of organic matter (72 to 82%) whereas the samples from the other two fuels, especially smokeless coal, contained much lower percentages (27% for smokeless coal sample; 55% for wood sample). Full-scan GC/MS analysis of the organic extracts of the smoky and smokeless coal combustion samples showed their major components to be PAH and methylated PAH, whereas the major components of the wood samples were hydroxylated aromatics, aliphatic aldehydes and alcohols, and PAH. Fewer PAH compounds were detected in the wood samples than in the coal samples. The results of the PAH analysis for selected carcinogenic compounds are shown in Fig. 3. The highest PAH levels were consistently found in the smoky coal samples from CG, followed by those from LB. The wood samples contained much lower levels of PAH, and the smokeless coal sample contained the lowest levels. The smoky coal samples also contained the highest levels of nitrogen heterocyclic compounds, for example, dibenz-[*a,j*]acridine: 688 ng/m^3 in the CG smoky

Table 2. Percentage of households burning smoky coal before 1958 and 1973–1975 unadjusted lung cancer mortality in 11 Xuan Wei communes.

Commune	Smoky coal (%)	Lung cancer mortality (per 100,000)
Cheng Guan	100.0	151.8
Lai Bin	89.7	109.3
Rong Cheng	81.9	93.0
Long Tan	78.0	32.1
Long Chang	76.1	33.2
Hai Dai	49.7	10.8
Pu Li	35.2	2.8
Ban Qiao	34.0	16.7
Luo Shui	2.7	1.8
Re Shui	0.0	2.3
Xi Ze	0.0	0.7

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coal sample, 7 ng/m^3 in the smokeless coal sample, and below the detectable limit in the wood sample. Filters in both the HV and MV samplers collected a wide range of PAH compounds (three to seven rings), whereas the XAD collected mostly compounds of four or fewer rings. The coal extracts contained a higher percentage of aromatic compounds (36 to 40%) than the wood sample extracts (7%). Most (76%) of the mass in the wood extract was in the polar fraction.

Most samples required metabolic activation to display significant mutagenicity (Table 3), which also suggested the presence of PAH. The CG smoky coal samples showed the highest mutagenic activity, followed by the LB smoky coal samples. The wood samples displayed lower activity, and the smokeless coal samples displayed the least. The aromatic and polar fractions of the smoky coal samples contributed most of the mutagenic activity. The aliphatic fractions (accounting for 1 to 5% of organic mass in the extracts) of all samples were nonmutagenic. All XAD samples displayed little mutagenicity.

The fractions that displayed the most mutagenic activity—the aromatic and polar fractions of the smoky coal samples—were subjected to GC/MS analysis to identify major components. The aromatic fractions consisted primarily of PAH, methylated PAH, and nitrogen heterocyclic compounds. The polar fractions of the smoky coal samples included nitrogen- and oxygen-containing compounds.

This study revealed that the residents of CG, where lung cancer rates are highest and the fuel is smoky coal, are exposed to very high indoor particulate concentrations [more than 100 times the proposed U.S. ambient air 24-hour standard for PM10 (*9*)]. The particles from smoky coal combustion were mostly organic and submicron—a size that stays longer in the air and can be effectively deposited in the lung after inhalation (*10*)—and contained high levels of carcinogenic PAH compounds. Indoor benzo[*a*]pyrene concentrations during cooking are comparable to occupational exposure levels, such as those in coke oven plants (*11*). Mutagenicity results were also consistent with the epidemiologic findings: the sample from CG showed the most mutagenic activity, followed by the sample from LB, the commune with the next highest lung cancer mortality; the samples from RS, the low-mortality commune, showed lower mutagenic activity.

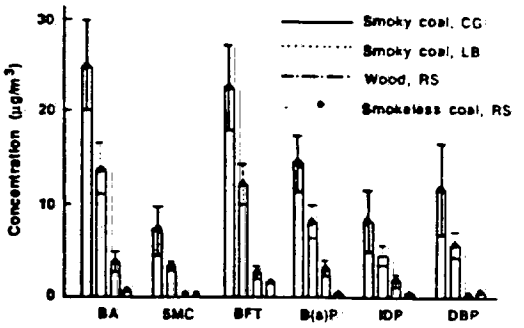

Fig. 3. Indoor polycyclic aromatic hydrocarbon concentrations by HV sampling (PM10). Values are mean (± SEM, where shown) of the compounds, showing sufficient evidence of carcinogenicity in animals (*6*). BA, benz[*a*]anthracene; 5MC, 5-methylchrysene; BFT, benzofluoranthenes; B(*a*)P, benzo[*a*]pyrene; IDP, indeno[1,2,3-*c*,*d*]pyrene; and DBP, dibenzo[*a*,*e*]pyrene. Each bar represents data from four homes of each commune, except the bar for smokeless coal. Smokeless coal data were from one home.

The differences, based on per cubic meter of air (Fig. 3 and Table 3), in PAH concentrations and mutagenicity of the CG and the LB homes were mainly due to the difference in the particulate concentrations during cooking (CG homes had 1.5 times higher particulate concentrations than LB homes). Based on per microgram of the organic mass extracted from the particles, the PAH and mutagenicity of samples from homes in these two communes were similar (2.6 and 3.3 revertants per microgram for CG and LB neat organic extracts, respectively, in contrast to 0.7 revertant per microgram for the RS sample). Differences in particulate concentration were mainly due to differences in cooking habits. The LB residents customarily cook only a breakfast (with a longer period of a more steady fire) and a supper each day, whereas the CG (and RS) residents usually cook three meals with shorter periods that require more frequent starting and stoking of the fire, and hence generate higher smoke emissions than a steady fire.

The aromatic fractions from coal combustion contained more methylated PAH compounds than the sample from wood combustion (for example, the ratios of 5-methylchrysene:chrysene were 0.27:1 in smoky coal, 0.10:1 in smokeless coal, and 0.04:1 in wood). Some methylated PAH compounds are known to be more carcinogenic than their parent PAH compounds (*6*). The high levels of methylated PAH compounds from smoky coal combustion may contribute to the high lung cancer rates in CG and LB. The presence of nitrogen heterocyclic compounds in the smoky coal combustion sample may also contribute to the high rates. We observed that, in addition to PAH, the polar compounds (accounting for 30% of the organic mass) also showed significant mutagenicity in the smoky coal samples.

This study, like other studies, suggested little association between domestic open-fire wood smoke and lung cancer (*12*). The less efficient lung deposition of the large particles from wood combustion plus the lower concentrations of biologically active compounds may both contribute to the low rate of lung cancer in RS, where wood is a common fuel. Smokeless coal, the other fuel used in RS, gave low indoor concentrations of particles of low organic content. Unlike the particles from smoky coal combustion, 90% of the particles from smokeless coal

Table 3. Mutagenicity of Xuan Wei indoor air particles (PM10). Data represent one home in each commune. The home selected was the one showing mutagenic activity in the neat sample close to the mean value of all four homes sampled in each commune.

Fraction	Mutagenicity (revertants × 10^3 per cubic meter)*			
	Smoky coal, CG	Smoky coal, LB	Wood, RS	Smokeless coal, RS
Neat sample	58.9 ± 6.8	17.0 ± 1.5	11.1 ± 0.5	1.3 ± 0.05
Aliphatics (hexane)	0	0	0	0
Aromatics (hexane/benzene)	18.1 ± 1.6 (30.7)†	6.7 ± 0.4 (39.4)	3.1 ± 0.2 (27.9)	0.5 ± 0.03 (38.5)
Moderately polar compounds (dichloromethane)	8.7 ± 0.8 (14.8)	4.0 ± 0.3 (23.5)	4.4 ± 0.2 (39.6)	0.3 ± 0.02 (23.1)
Polar compounds (methanol)	24.4 ± 1.4 (41.4)	7.9 ± 0.3 (46.5)	5.0 ± 0.5 (45.0)	0.4 ± 0.03 (30.8)

*Results from high-volume sampling. The organic extracts of the particulate samples were solvent-exchanged to dimethyl sulfoxide and tested at a minimum of five doses in triplicate. A sample was considered mutagenic if a dose-response relation was observed. The slope of the initial linear portion of each dose-response curve was calculated by least-squares linear regression to obtain the number of revertants per microgram of organics. The number of revertants per cubic meter of air was calculated by multiplying the number of revertants per microgram of organics by the micrograms of organics per cubic meter of air. Standard errors of slopes are also shown. †Numbers in parentheses represent the percentage of the neat sample.

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combustion were soot and unburned fuel. These may also explain the lower rate of lung cancer in RS.

Thus, to date, the collaborative studies of Xuan Wei lung cancer have shown consistency among epidemiologic, physical, chemical, and toxicologic findings. The accumulating data increasingly suggest an etiologic link between indoor smoky coal burning and lung cancer.

Note added in proof: In our recent mouse skin tumor initiation promotion studies in female SENCAR mice using the organic extract as the tumor initiator and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) as the promoter, the organic extract of the smoky coal sample induced more papillomas per mouse at the dose of 10 mg per mouse (7.5 papillomas after 26 weeks of promotion) than the extract of the wood sample (2.1 papillomas). When applied dermally twice weekly (total 2 mg per mouse per week) to the mice without TPA promotion, the smoky coal sample induced carcinomas in 35% of the treated animals while no carcinomas were observed in the wood sample–treated mice or in the solvent control-treated mice after 52 weeks of the treatment (*13*).

REFERENCES AND NOTES

1. Editorial Committee for the Atlas of Cancer Mortality in the People's Republic of China, *Atlas of Cancer Mortality in the People's Republic of China* (China Map Press, Shanghai, 1979).
2. Office of Tumor Preventive Research, Department of Public Health, the People's Republic of China, in *Investigation and Research of Chinese Cancer Mortality Rates* (People's Public Health, Beijing, 1979), chap. 7, pp. 148–174.
3. ASTM D3172-73, D3176-74, D3682-78, and D388-77, in *1978 Annual Book of ASTM Standards, Part 26. Standards and Tentatives Relating to Gaseous Fuels; Coal and Coke; Atmospheric Analysis* (American Society for Testing and Materials, Easton, MD, 1978).
4. B. A. Petersen and J. C. Chuang, in *Toxicological Effects of Emissions from Diesel Engines*, J. Lewtas, Ed. (Elsevier, New York, 1982), pp. 51–67.
5. M. G. Nishioka, B. A. Petersen, J. Lewtas, in *Chemical Analysis and Biological Fate: Polynuclear Aromatic Hydrocarbons*, M. Cooke *et al.*, Eds. (Battelle, Columbus, OH, 1982), pp. 603–612.
6. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (International Agency for Research on Cancer, Lyon, 1983); vol. 32, part 1, pp. 95–447.
7. B. W. Ames, J. M. McCann, E. Yamasaki, *Mutat. Res.* 31, 347 (1975).
8. L. D. Claxton, *Environ. Int.* 5, 389 (1981).
9. *Federal Register* (20 March 1984), p. 10416.
10. G. L. Fisher and D. F. S. Natusch, in *Analytical Methods for Coal and Coal Products*, C. Karr, Jr., Ed. (Academic Press, New York, 1979), vol. 1, pp. 489–541.
11. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (International Agency for Research on Cancer, Lyon, 1983); vol. 34, part 3, pp. 107–109.
12. H. W. de Koning, K. R. Smith, J. M. Last, *Biomass Fuel Combustion and Health* (WHO EFP/84.64, World Health Organization, Geneva, 1984).
13. J. L. Mumford, C. T. Helmes, S. Nesnow, unpublished data.

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Preferred Microtubules for Vesicle Transport in Lobster Axons

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The hypothesis that transported vesicles are preferentially associated with a subclass of microtubules has been tested in lobster axons. A cold block was used to collect moving vesicles in these axons; this treatment caused the vesicles to accumulate in files along some of the microtubules. Quantitative analysis of the number of vesicles associated with microtubule segments indicated that lobster axons have two distinct populations of microtubules—transport microtubules that are the preferred substrates for vesicle transport and architectural microtubules that contribute to axonal structure.

MICROTUBULES ARE THE LINEAR substrates for vesicle transport in axons (*1–3*); in addition to their role in vesicle transport, they are essential structures in axonal architecture (*4*). These two functions—transport and architecture—place different demands upon the microtubules. In some cases, the requirements of architecture actually appear opposite to those of vesicle transport. For example, axonal microtubules have an extensive system of sidearms that contribute to the architecture of the axonal cytoskeleton by linking the microtubules to neighboring cytoskeletal structures (*5*). Although such cross-links help to define axonal architecture, they offer potential resistance to the movement of transported vesicles along the microtubules (*6*).

There and other differences between the requirements of vesicle transport and architecture may have fostered the evolution of two classes of microtubules—one class that is the preferential substrate for vesicle transport and another class that contributes primarily to axonal architecture. To examine the possibility that axons contain a subclass of microtubules that are the preferred substrates for vesicle transport, we analyzed the distribution of transported vesicles in lobster axons. In lobster axons, microtubules are the only long polymers (*7*). These axons, and those of other arthropods, lack neurofilaments; arthropods may have lost the genes for neurofilament proteins when the arthropod lineage diverged from the other metazoan phyla (*4, 8*). In arthropod axons, microtubules fulfill all of the architectural and transport functions required of cytoskeletal polymers in axons.

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To determine whether transported vesicles moved preferentially along particular microtubules in lobster axons, we used the cold-block method to collect and distinguish transported vesicles. A small region of the axon is cooled to 2° to 4°C (*3, 9, 10*). When moving vesicles reach the cold block, they stop and accumulate along the normal pathways of transport (*3, 9, 10*). In vertebrate and molluscan axons (both of which contain neurofilaments), the transported vesicles accumulate in files along microtubule domains, which are surrounded by neurofilaments; these microtubule domains are the

Table 1. Vesicle distribution among lobster axon microtubules assuming one homogeneous population of microtubules. Total vesicles, 346; average vesicles per microtubule, 1.18.

Vesicles per microtubule	Microtubules (number)	
	Observed*	Poisson prediction (m = 1.18)
0	212	90
1	14	106
2	11	63
3	9	25
4	10	7
5	12	2
6	8	0
7	8	0
8	4	0
9+	5	0
Total	293	293

*Observed and expected values are statistically distinct by both the chi-square test and the Kolmogorov-Smirnov test ($P < 0.01$).

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The Epidemiology of Lung Cancer in Xuan Wei, China: Current Progress, Issues, and Research Strategies

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ABSTRACT. In Xuan Wei, a rural Chinese county of about one million people, females' annual lung cancer mortality is China's highest, and males' is among China's highest. Xuan Wei's very high indoor air pollution levels (sometimes exceeding 20 mg/m³), residentially stable population, relatively uncomplicated lifestyle, and wide geographic variation in lung cancer mortality render it highly amenable to quantitative, interdisciplinary investigation of chemical carcinogens due to indoor air pollution. To date, epidemiologic findings reveal a closer association of lung cancer with the indoor burning of "smoky" coal (as opposed to "smokeless" coal or wood) than with tobacco use or occupation. Current aerometric, chemical, and toxicologic findings tend to confirm this association, though the specific carcinogenic constituents of Xuan Wei indoor air pollution have not yet been determined. Chinese and American investigators are conducting interdisciplinary field and laboratory investigations to quantify the lung cancer risk attendant on indoor air pollution relative to other factors, to measure and compare the characteristics of pollution from different Xuan Wei fuels, to determine the relative etiologic importance of pollution composition and concentration, and to develop quantitative relationships between air pollution dose and lung cancer risk.

XUAN WEI COUNTY, in northeastern Yunnan Province, China, is 6,257 km² and lies on high plateau punctuated by mountain ridges. Its total population is about one million people, over 90% of whom belong to China's predominant ethnic group, the Han. Xuan Wei is rural—over 90% of residents are farmers—and until the 1980s was relatively untouched by modernization. Nonagricultural occupations include homemaking, coal mining, office work, and industrial work in chemical fertilizer plants, two coal-fired electric power plants (including one of Yunnan's largest), and a cement products plant. All of these plants were built after 1960.

Xuan Wei has 20 communes with populations of about 30,000 to 60,000. Each commune is divided into

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"large production teams," of which there are 385 in the County. Each large team is further divided into 15 to 25 "small production teams." The population is residentially stable; fewer than 20% of households experienced in- or out-migration from 1965 to 1985. Xuan Wei is well known for its export of ham, though the typical local diet consists of corn, potatoes, rice, and about 400 g of unsmoked pork per week.

Tobacco smoking is very rare in Xuan Wei females but common in males. Factory-made cigarettes and locally grown tobacco are used. Cigarettes are frequently smoked through water pipes. Tobacco is seldom used orally or nasally. For generations, Xuan Wei residents have used three major fuel types, "smoky" coal, "smokeless" coal, and wood, for home heating and cooking. Smoky coal is glossy black, has a low sulfur content, and smokes heavily on firing. Smokeless coal is dull black, has high sulfur and ash contents, and produces little smoke. Because smokeless coal is powdery, it is usually mixed with clay to form briquets prior to burning.

Most Xuan Wei residents live in mud-brick or wooden two-story homes in which the cooking, dining, and living area is downstairs and the sleeping area is upstairs. The average household contains about five people, including children, parents, and often grandparents. Women generally start the domestic fire in the morning and prepare the two or three daily meals eaten at home, while men spend most daylight hours outside the home. Females generally start cooking at about age 12. Domestic fuel has traditionally been burned in a shallow, unvented pit in the floor of the dwelling's main room.

Lung cancer in Xuan Wei

Annual unadjusted and adjusted lung cancer mortalities in China, the U.S., Yunnan Province, and Xuan Wei are presented in Table 1.[1] In the Table, as throughout this report, the term "lung cancer" includes carcinomas of lung, bronchus, and trachea. During 1973–1975, males' and females' lung cancer mortalities in Yunnan Province were 19th and 25th, respectively, among China's 29 provinces, municipalities, and autonomous regions.[2] In marked contrast, females' rates in Xuan Wei were higher than in any other Chinese county, and males' rates were among China's highest. Males' and females' absolute mortalities were similar, a surprising finding in view of the rarity of smoking in women. In the Chinese national cancer survey of 1973–1975, lung cancer was the only type of cancer for which mortality in Xuan Wei exceeded the national average. Of 115 tumor specimens examined pathologically in Xuan Wei, 58% were squamous cell carcinomas, 28% were adenocarcinomas, and the remainder were mixed cell, undifferentiated, or alveolar carcinomas.[3]

The marked difference in lung cancer mortality among Xuan Wei communes was especially striking. This difference is apparent in Table 1, and Figure 1 shows a map of Xuan Wei County with commune boundaries, annual unadjusted lung cancer mortalities in each commune, and locations of mines supplying smoky and smokeless coal for domestic use. That commune population denominators are reasonably large, and that vigorous lung cancer surveillance is conducted throughout the County, strongly suggest that

Table 1.—Annual Lung Cancer Mortality Rates in China and the U.S.

Place and time period	*Lung cancer mortality rate, per 100,000*					
	Unadjusted		Age-adjusted to 1964 China population		Age-adjusted to 1970 U.S. population	
	Males	Females	Males	Females	Males	Females
China 1973–1975	5.0*		6.8	3.2	12.3	5.7
U.S. 1970	53.7	12.0	30.0	6.3	53.7	12.0
Yunnan Province 1973–1975	2.8*		4.3	1.5	6.9	2.5
Xuan Wei County 1973–1979	27.0	24.5	27.7	25.3	43.2	38.7
Three Xuan Wei communes of highest lung cancer mortality (Cheng Guan, Lai Bin, Rong Cheng) 1973–1979	114.4	120.6	118.0	125.6	186.8	193.4
55–59 yr age group in high-mortality communes	849.4	904.0				
Three Xuan Wei communes of low lung cancer mortality (Pu Li, Yang Liu, Re Shui) 1973–1979	4.0	2.8	4.3	3.1	5.8	4.3
55–59 yr age group in low-mortality communes	17.1	18.1				

*Unadjusted rate for both sexes combined.

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the observed intercommune variation in lung cancer mortality is real.

On balance, Xuan Wei constitutes a very unusual natural experiment in lung cancer production. The marked local variation in the dependent variable (lung cancer mortality) presents a rare opportunity to investigate the relative etiologic roles of independent variables (known and suspected risk factors). That such important independent variables as population mobility and lifestyle are reasonably well "controlled" further enhances Xuan Wei as a setting for quantitative, interdisciplinary investigation of lung cancer etiology. Since the 1970s investigators from Beijing and Yunnan Province have conducted epidemiologic, aerometric, toxicologic, and chemical studies in Xuan Wei. In 1982 they were joined by investigators from the U.S. Environmental Protection Agency.

Overview of current evidence

Data gathered to date in Xuan Wei disclose a stronger association of lung cancer with domestic coal use than with any other risk factor so far assessed, including tobacco smoking. As shown in Figure 1, in communes with smoky coal mines (including Cheng Guan [CG] and Rong Cheng [RC], most of whose residents use smoky coal from Lai Bin [LB] commune), the average annual lung cancer mortality in 1973–1975 was 35 per 100,000, in contrast to an average of 4 per 100,000 in communes without smoky coal mines. Also, in 1982 Chinese investigators conducted a survey of fuel use and tobacco smoking in 11 Xuan Wei communes. The proportion of households in each commune using smoky coal before 1958 was highly correlated with commune-specific lung cancer mortality between 1973 and 1975 ($r = 0.82$, $p = .002$).

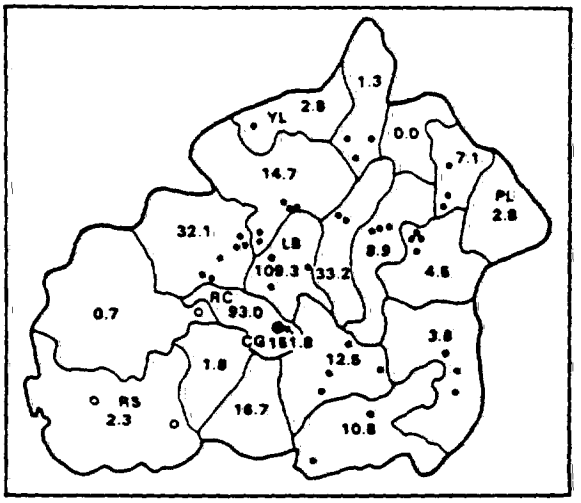

Fig. 1. Map of Xuan Wei County, showing commune boundaries, each commune's unadjusted annual lung cancer mortality rate per 100,000 (both sexes, 1973–1975), and mines supplying domestic coal: (●) smoky coal and (○) smokeless coal. Designated communes: CG, Cheng Guan; LB, Lai Bin; PL, Pu Li; RS, Re Shui; RC, Rong Cheng; and YL, Yang Liu. (Science 1987, 235:217–220. Copyright 1987 by the AAAS. Reprinted with permission.)

Table 2 shows 1982 survey results for two Xuan Wei communes, LB and Re Shui (RS), with very different lung cancer mortality rates. Sex-specific smoking habits differed little between the two communes (indeed, somewhat more males had smoked in RS), but fuel use habits differed greatly, with nearly all of LB, and none of RS, using smoky coal. In a previous survey,[3] higher lung cancer rates were detected in farmers than in coal miners or office workers, tending to exclude nonagricultural occupations as an important lung cancer risk factor.

In 1983, indoor air was sampled in Xuan Wei homes in which smoky coal, smokeless coal, and wood were burned. Concentrations of particulates and total organics (dichloromethane-extractable portion of particulate samples) were measured. Total organic samples and chemical fractions thereof were also subjected to Ames testing (Tables 3 and 4). Extremely high levels of particulates and total organics were observed in homes burning smoky coal and wood (Table 3); levels during smokeless coal burning were considerably lower

Table 2.—Results of 1982 Survey of Smoking and Fuel Use in Two Xuan Wei Communes with High and Low Lung Cancer Mortality Rates

	Commune	
	Lai Bin	Re Shui
Population	60,000	60,000
Unadjusted annual lung cancer mortality rate per 100,000 1973–1975	109.3	2.3
Percentage of population ever smoking tobacco		
Males	44.02%	49.05%
Females	0.05	0.07
Percentage of population using		
Smoky coal	89.7%	0.0%
Smokeless coal	1.6	33.4
Wood	8.7	66.6

Table 3.—Mean Indoor Air Pollution Levels (mg/m³) in Xuan Wei, 1983, by Type of Fuel Burned

	Suspended particulates* (mg/m³)	Dichloromethane-extractable organics (mg/m³)
Smoky coal (Cheng Guan)	24.4	17.6
Smoky coal (Lai Bin)	9.5	7.8
Wood (Re Shui)	22.3	12.3
Smokeless coal (Re Shui)	1.8	0.5

*Suspended particulates as measured by high-volume sampler with an air flow rate of 40 ft³/min, equipped with a head designed to exclude half of particles of 10 μm diameter.

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Table 4.—Ames Test Mutagenic Potency of Total Organics and Organic Fractions* of Xuan Wei Indoor Air Pollution, 1983, by Type of Fuel Burned

	Potency (revertants × 1000 per mg of sample)			
	Smoky coal (Cheng Guan)	Smoky coal (Lai Bin)	Wood (Re Shui)	Smokeless coal (Re Shui)
Total organic sample	2.6	3.3	0.9	2.6
Organic fractions				
Aliphatic	0	0	0	0
Aromatic	2.1	3.2	3.4	2.5
Moderately polar	1.4	2.4	2.6	3.0
Polar	4.0	5.6	0.5	2.0

*Organic fractions were extracted with different solvents, as follows: aliphatic, hexane; aromatic, hexane/benzene; moderately polar, dichloromethane; polar, methanol.

(though still high by U.S. standards). Levels of individual polycyclic aromatic hydrocarbons, including benzo(a)pyrene, were generally highest during smoky coal burning, intermediate during wood burning, and lowest during smokeless coal burning. In the smoky and smokeless coal samples, most organics were in the aromatic (hexane/benzene-extractable), moderately polar (dichloromethane-extractable), or polar (methanol-extractable) fractions. Aliphatic (hexane-extractable) concentrations were relatively low for all fuel types.

The Ames test mutagenicity (revertants per cubic meter of air) of total organic combustion samples from smoky coal was considerably higher than that of smokeless coal or wood samples.[1] The mutagenic potency (revertants per milligram of sample) of organic smoky and smokeless coal samples was higher than that of wood samples (Table 4). The potency of the polar fraction was highest in smoky coal combustion samples and lowest in wood samples, but the potency of each of the other organic fractions did not differ greatly among the three fuel types. On balance, differences in mutagenic potency among the fuel types were not as great as differences in lung cancer mortality among the communes using the different fuel types.

A case-control study is currently in progress in Xuan Wei. In this study each lung cancer patient is matched for age and sex with a control subject whose residence is selected randomly from throughout the County. Interim findings from the first 39 case-control pairs of females and 33 pairs of males are presented in Tables 5 and 6. Among females, there were no smokers 10 yr prior to the study. Among males, the majority of cases and controls had been smokers (Table 5), leaving few discordant pairs for consideration. At the same time, the number of controls smoking heavily, 21, was larger than the corresponding number of cases, 15. These observations suggest that smoking may not be as serious a lung cancer risk factor in Xuan Wei as in numerous other locations.

If length of using smoky coal were positively associated with risk of lung cancer, one would expect the odds ratio associated with smoky coal use to increase with increasing remoteness in the time at which smoky coal was used. In the interim case-control distributions,

Table 5.—Interim Distribution of Cigarette Smoking 10 yr Prior to Study in 33 Male Case-Control Pairs in Xuan Wei

	Cases		
	Not smoke	L.E. 16 cigarettes/day	>16 cigarettes/day
Controls			
Not smoke	2	0	2
L.E. 16 cigarettes/day	0	6	2
>16 cigarettes/day	3	7	11

Table 6.—Interim Odds Ratios Associated with Smoky Coal Use Now, 20 yr Ago, and at Age 12 in Xuan Wei Lung Cancer Patients and Controls

Time using smoky coal	Males (33 pairs)	Females (39 pairs)
Now	1.5	2.6
20 yr ago	1.3	2.9
At age 12	4.0	3.7

such a trend was observed in both sexes (Table 6). However, the absolute magnitudes of the odds ratios were not as great as might have been expected in light of evidence summarized above. Because females customarily spend much more time than males near the domestic fire, one might expect smoky coal-associated ratios to be substantially higher in females; in fact, the interim odds ratios did not differ greatly by sex.

Epidemiologic issues and research goals

Though available findings reveal a definite relationship between smoky coal use and lung cancer in Xuan Wei, the relationship is by no means fully characterized as yet. It will be necessary to gather further information on four interrelated levels. The first-level goal is to quantitate the importance of smoky coal use relative to

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other known and suspected risk factors. On this level, several important questions must still be addressed. For example, the unexpectedly small odds ratios associated with smoky coal use and small etiologic impact of tobacco smoking remain to be confirmed and explained.

The second-level goal is to determine the similarities and differences among the combustion products of fuels, including different smoky coals, used in different Xuan Wei communes. While communes with smoky coal mines generally have higher lung cancer rates than communes without them, rates vary greatly even among communes with smoky coal mines. This variation is probably not fully explained by historical differences in fuel use from commune to commune. Instead, it appears probable that the generic term "smoky coal" encompasses a set of coals which differ geographically in composition and combustion products, and whose combustion products may confer different risks of lung cancer. Indeed, the observed differences in pollution levels during smoky coal combustion in CG and LB communes (Table 5) suggest that different smoky coals vary in at least the concentrations of their combustion products.

The third-level goal is to determine and compare the etiologic importance of the dose (or concentration) and chemical/physical composition of indoor air pollution in Xuan Wei. It is conceivable that certain Xuan Wei coals produce lung cancer because their combustion products contain carcinogens not found elsewhere in the County. It is also possible that the composition of different coals' combustion products is similar, and that lung cancer is related primarily to differences in pollution dose emitted by different coals. Of course, risk may well be a complex function of both composition and concentration. The observed similarity in mutagenic potency between smoky and smokeless coal combustion products (Table 4) suggests that pollution concentration is an etiologically important factor, but by no means eliminates the possibility that Xuan Wei coals exhibit important differences in composition.

The fourth-level goal is to develop quantitative relationships between pollution dose and the likelihood of developing lung cancer. Such relationships will maximize the contribution of the project to the risk assessment process. The most appropriate functional form of these relationships cannot be determined until the relative etiologic importance of indoor air pollution and other risk factors is known, until combustion products of different Xuan Wei fuels have been more fully characterized and compared, and until the relative importance of pollution composition and concentration has been more thoroughly assessed.

Research strategies

To exploit fully the learning opportunities offered by the Xuan Wei project, Chinese and American investigators have mounted an interdisciplinary research program to accomplish project goals. The program incorporates epidemiology, environmental measurement, chemistry, and toxicology. Field and laboratory investigations are closely linked. In addressing the different goals, the various disciplines are employed as described below.

In addressing the first-level goal, determination of the etiologic importance of domestic fuel use relative to other risk factors, epidemiology assumes the major role. Cross-sectional questionnaire surveys and a case-control study are being conducted. The main purpose of the cross-sectional surveys is to measure and compare the distributions of fuel use and other risk factors in communes with different lung cancer mortalities. Survey results will allow qualitative inference as to the relative importance of the risk factors. For instance, the observation that factors other than fuel use were distributed similarly in high- and low-mortality communes would tend to underscore the etiologic importance of fuel use.

The case-control study is intended to quantitate the etiologic importance of fuel use relative to other risk factors. Lung cancer patients and controls, selected as described above, are queried in detail about fuel use history, tobacco use history, occupational history, socioeconomic status, diet, family medical history, and other factors. Logistic regression will be employed to determine the adjusted lung cancer risk attendant on each of the factors studied.

All disciplines are closely integrated to accomplish the second-, third-, and fourth-level research goals described above. Field and laboratory investigations are both used to compare the compositions and concentrations of fuel combustion products. Laboratory conditions have been designed to simulate field conditions as closely as possible. Field studies allow direct linkage of environmental measurements to epidemiologic information. Laboratory studies allow more detailed measurement of combustion products, including short-lived and volatile species, than can be performed in the field.

In the Xuan Wei project, pollution samples collected in the field and the laboratory are often subjected to toxicologic assay. Comparison of biologic activities yields clues as to the relative etiologic importance of combustion products from different fuels. Toxicologic assay of different chemical fractions also allows inference as to the relative etiologic importance of pollution composition and concentration. Furthermore, toxicologic testing provides an assessment of the relative ability of different types of assay to predict human experience with lung cancer.

The results of first-, second-, and third-level investigations will all contribute to the development of quantitative relationships between air pollution dose and lung cancer response. First-level studies are expected to identify epidemiologic covariates that must be considered in the construction of dose-response functions. The reliability and specificity of these functions will depend largely on the outcome of second- and third-level studies. For example, these studies may show that the combustion products of various Xuan Wei fuels are chemically and physically similar, and differ only in the concentrations of pollutants generated. If so, dose-response functions may be reliable but not specific as to the relative etiologic impact of individual pollution constituents. On the other hand, if pollution composi-

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tion and concentration are both shown to vary across different Xuan Wei fuels, it may be possible to develop dose-response functions that are both reliable and specific. In any event, the Xuan Wei project is expected to generate new and useful evidence as to the influence of indoor air pollution on lung cancer production.

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We are grateful for the essential contribution made by the Yunnan Province and Xuan Wei County Antiepidemic Stations. We thank Chongwang Xu of the Xuan Wei County Antiepidemic Station for compiling unadjusted lung cancer mortality rates. We are grateful to Shouren Cao of the Institute of Environmental Health and Engineering, Beijing, for collaboration in collecting Xuan Wei air pollution samples. We thank Marcus Cooke and Jane C. Chuang of the Battelle Columbus Division for chemical analyses of pollution samples.

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References

1. Mumford, J. L.; He, X. Z.; Chapman, R. S.; Cao, S. R.; Harris, D. B. et al. 1987. Lung cancer and indoor air pollution in Xuan Wei, China. *Science* 235:217–20.
2. Li, J. Y. et al., Eds. 1979. *Atlas of Cancer Mortality in the People's Republic of China*. First ed. Shanghai: China Map Press.
3. The Coordinative Group of Lung Cancer in Xiangwei (Xuan Wei) District, 1979. *Yunnan Medical Journal*, volume 16.

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INDOOR AIR POLLUTION AND WOMAN LUNG CANCER

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The death rate (per 100,000) of woman lung cancer has increased from 17.8 (1976) to 24.7 (1985) in Guangzhou. The woman smoking rate is only 3.9 %, but over 80 % of woman who died from lung cancer had done domestic cooking frequently during their lifetime. The concentrations of air pollutants (SO_2 , NOx, total suspended particulates, sedimentary dust, B(a)P, radon, thoron and their daughters) indoor was higher than outdoor, and they main source come from domestic cooking in downtown. Besides, the levels of woman urine-B(a)P cooking used coal were higher than those cooking used gas. It suggests that coal burning for cooking might be a cause for inducing woman lung cancer.

INTRODUCTION

Lung cancer is one of the major health problems worldwide. Over the past three decades the death rate from lung cancer has increased rapidly in both the developed and developing countries. Especially noteworthy is the marked increase of woman lung cancer.

Although the cause of lung cancer is better understood than other malignant neoplasms, reports from different studies are quite variable. Andrews (1985) reported that smoking is a major causal factor of lung cancer in woman in the United States. Ayiomamitis (1985) also points out that recent trends towards increased use of tobacco products may account for the drastic increase in female rate in Canada. However, the percentage of smokers among woman with lung cancer in Italy was shown to be only 29 % (Sammartino, 1985). Svensson (1985) suggests that indoor exposure to Radon and Radon daughters from ground emissions may be related to bronchial cancer among women in Stockholm and smoking habits did not appear to be a major confounding factor for this disease. The incidence rate of lung cancer among women in Xiangwei,a county of China, is very high and they do not smoke at all (Zhao,1985).

For the purposes of further identifying the lung cancer associated factors,Guangzhou lung cancer deaths occurring between

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1980 and 1985 were reviewed. This motality data was analyzed along with data on indoor and outdoor air pollution.

MATERIALS AND METHODS

Accurate reports on the number of death from malignant neoplasms were obtained from the city cremation station, over 95 % of deceased Guangzhou residents are cremated, and from local police stations where relatives must cancel the deceased's name from police records and report the cause of death. Health bureau personnel interview relatives using a uniform questionnaire which is then completed by reviewing hospital clinic records.

Indoor air quality was investigated in 20 homes located in downtown Guangzhou. The measured pollutants included SO_2 , NOx, TSP and B(a)P. Samples of SO_2 and NOx were collected at 2-hour intervals from 7:00 am to 7:00 pm for five consecutive days each season. TSP and B(a)P were measured once a day on the same five days each season. Outdoor air quality data were obtained from the Global Atmospheric Monitoring Station of the World Health Organization (WHO), which was founded in 1980 in Guangzhou city.

The level of radioactivity of indoor and outdoor were investigated in 40 homes twice a year in summer and winter, the indoor data was analyzed along not only with construction materials but also with cooking fuels.

Indoor air pollution comes maily from domestic cooking in Guangzhou. For further study the relationship between the kitchen air pollutants and their effects on body, the level of TSP, TSP-B(a)P, SD, SD-B(a)P in 72 homes and the concentrations of urine-B(a)P in 44 woman homemakers, living at the corresponding homes and never smoking, have been investigated.

A case control study was carried on 662 lung cancer deaths, this number was about 82% of total lung cancer deaths in 1985, and 662 non-lung cancer deaths. Matched for sex (M 446, F 216) age (± 2 year) and living places. The relative risks (odds ratios) for smoking and for coal fumes exposure were analyzed.

RESULTS & DISCUSSION

Mortality data for 3,305 cases of lung cancer (M 2,178, F 1,079) were collected between 1980 and 1985. It is estimated that over 95 % of all deaths due to lung cancer during that period in downtown Guangzhou were recorded.

Total and percentages by cigarettes per day of male and female with lung cancer are shown in Table 1. The percentage of non-smoking lung cancer cases among males is only 6.7 %, but among females it is as hgh as 41.4%,and 54% of them did not smoke themselves also had no exposure to other smokers during their lives.

Table

Cigarettes per day
1-
10-
20-
30-
40-
No smoking
Total

In 1982 there we
Guangzhou, this m
1982 Guangzhou cen
Ratios(SMR) by Job
shown in Table 2.
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Job, however the h

Table 2 DEATH RATE A

Occupation
Homemaker
Chemist
Machine repairman
Cargo handler
Cook
Construction worke
Salesclerk
Office worker
Teacher
Engineer
Doctor
Waiter/waitress
Total

s : P< 0.01

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Table 1. SMOKING HISTORY IN 3,305 LUNG CANCER DEATHS IN GUANGZHOU, CHINA (1980-1985)

Cigarettes per day	Male		Female	
	No.	%	No.	%
1-	77	3.54	92	8.53
10-	365	16.76	206	19.09
20-	927	42.56	223	20.67
30-	348	15.98	67	6.21
40+	314	14.42	44	4.08
No smoking	147	6.74	447	41.42
Total	2,178		1,079	

In 1982 there were 601 cases who died from lung cancer in Guangzhou, this mortality data was analyzed along with data on 1982 Guangzhou census. The death rate and Standard Mortality Ratios(SMR) by job (above 10 years) of lung cancer deaths are shown in Table 2. In general, the incidence of lung cancer among blue-collar workers is higher than for those with white-collar Job, however the highest job SMR in females is homemaker.

Table 2 DEATH RATE AND SMR BY JOB OF LUNG CANCER DEATHS IN GUANGZHOU, CHINA (1982)

Occupation	Death rates (per 100,000)		S M R	
	M	F	M	F
Homemaker	112.3	112.1	328	1078 *
Chemist	146.4	73.4	880 *	842 *
Machine repairman	103.4	13.3	769 *	294
Cargo handler	127.4	93.0	490 *	1051 *
Cook	186.3	40.0	588 *	335 *
Construction worker	131.5	0.0	491 *	0
Salesclerk	121.0	39.5	300	360 *
Office worker	84.5	46.1	155 *	266 *
Teacher	34.2	44.5	73	352 *
Engineer	38.9	10.1	100	120
Doctor	25.7	5.1	66	47
Waiter/waitress	25.7	10.9	45	23
Total	92.4	49.1		

* : P< 0.01

For comparison, Table 3 shown both indoor and outdoor levels of SO_2, NOx, TSP and B(a)P for 1984. Atmospheric sampling stations are near the houses where the indoor air quality was monitored. The results demonstrate that indoor air pollution is more severe than outdoor pollution, especially in B(a)P levels. Table 4 shown the comparison of radioactivity level between indoor and outdoor, the concentration of radon, thoron and their daughters indoor also higher than outdoor, especially in thoron, but all of them

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are under the China Basic Standards for Radiological Protection (GB 479-84). (radioactivity data from Wu Zenghan)

Table 3. COMPARISON OF AVERAGE LEVELS OF SO_2 , NOx, TSP AND B(a)P BETWEEN INDOOR AND OUTDOOR IN GUANGZHOU (1984)

	SO_2 ($\mu g/M^3$)	NOx($\mu g/M^3$)	TSP($\mu g/M^3$)	B(a)P($\mu g/100M^3$)
Indoor	190±80	70±30	210±70	1.30±0.98
Outdoor	80±20	40±10	200±30	0.50±0.26

Table 4. COMPARISON OF CONCENTRATIONS OF RADON, THORON AND THEIR DAUGHTERS BETWEEN INDOOR AND OUTDOOR IN GUANGZHOU

	Radon (Bq/M^3)	Radon daughter (10^{-6} J/M^3)	Thoron (Bq/M^3)	Thoron daughter (10^{-6} J/M^3)
Indoor	17.8±2.1	5.84±0.72	37.0±7.2	6.94±1.06
Outdoor	13.3±2.1	4.86±0.33	14.5±2.6	4.72±0.62
GB 4792-84	3300.0	19.0	75.0	57.0

Table 5 shown the indoor radioactivity levels in different constructive materials and different cooking fuels. The results demonstrated that green brick wall higher than red brick, brick floor higher than cement floor, and coal burning higher than gas burning.

Table 5. THE INDOOR RADIOACTIVITY LEVELS IN DIFFERENT CONSTRUCTION MATERIALS AND DIFFERENT COOKING FUELS

	No.	Radon(Bq/M^3)	Thoron(Bq/M^3)	P-value
Green brick	13	17.6±4.4	42.9±15.3	
Red brick	64	17.6±4.8	35.9±19.3	
Brich floor	37	18.5±4.0	43.5±16.1	P <0.01
Cement floor	21	17.6±4.8	29.3±14.2	
Coal burning	49	18.6±4.1	42.5±19.4	P <0.01
Gas burning	31	16.6±5.1	28.3±13.1	

Seasonal trends of daytime indoor SO_2 and NOx measurements for the 20 homes surveyed are shown in Fig. 1. There are three peaks of concentration of SO_2 and NOx at 7, and 11 am and at 7 pm. The winter curves are higher than for the other seasons. It is suggest that the main source of this pollution was come from domestic cooking.

A comparison of the kitchen air pollution and woman urine-B(a)P between briquette coal and liquefied petroleum gas burning kitchen are shown in Table 6. Since 1960 briquette coal is commonly used by Guangzhou residents in stoves without chimney. It

Table 6 COMPARIS
URINE-B(a)P BI

Total suspended Partic
TSP-B(a)P($\mu g/100M^3$)
Sedimentary dust(gm/M^2
SD-B(a)P($\mu g/M^2$ /Month
Urine-B(a)P(ng/l)

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The results of ca
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increase in the s
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Table 6 COMPARISON OF THE CONCENTRATIONS OF TSP, TSP-B(a)P SD,SD-B(a)P AND URINE-B(a)P BETWEEN THE COAL BURNING KITCHEN AND GAS BURNING KITCHEN

	Briquette coal burning kitchen		Liquefied Petroleum gas burning kitchen		P-value
	No.	X±SD	No.	X±SD	
Total suspended Particulates(μg/M³)	37	322±131.0	27	188±6.70	P <0.01
TSP-B(a)P(μg/100M³)	21	11.9±9.3	21	2.2±1.8	P <0.01
Sedimentary dust(gm/M² /Month)	37	11.9±8.4	24	5.4±2.9	P <0.01
SD-B(a)P(μg/M² /Month)	28	11.1±8.4	12	2.2±1.7	P <0.01
Urine-B(a)P(ng/l)	24	4.0±1.8	20	2.8±1.5	P <0.05

caused severe indoor air pollution not only, but also resulting homemakers urine-B(a)P increased.

The results of case control study are shown in Table 7. Both the Mantel-Haenszel test and the stratification analysis unanimously indicate that smoking for male and coal fumes exposure for female were the risk factors for inducing human lung cancer.

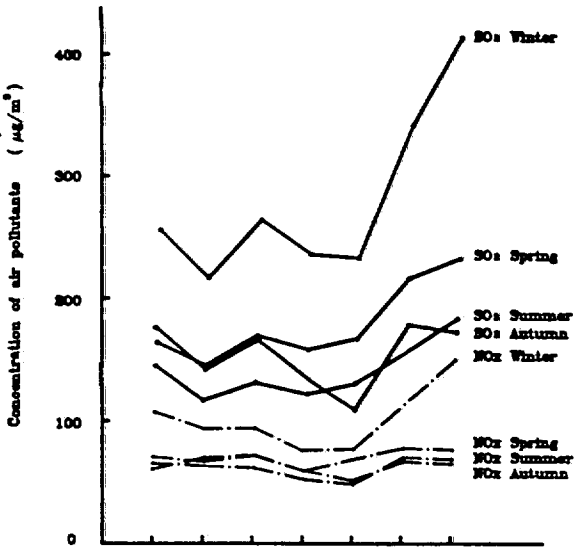

Fig.1 INDOOR SO_2 AND NOx DURING THE DAYTIMES IN FOUR SEASONS FOR TWENTY FAMILIES IN GUANGZHOU, CHINA (1984-1985)

Lung cancer death rate has increased rapidly in worldwide suggesting there are some new exogenous factors related to lung cancer have been introduced into human environment, and this factors might be existence in whole world. Smoking, occupational exposure and atmospheric pollution including radioactivity pollution have been reported as the relative factors, however, in some countries high incidence of lung cancer and low smoking rate can be occurred. Occupational exposure can only be used to explain the incidence increase in the special population, e.g. chromate workers,but not to explain lung cancer among the general population in an urban area. A stable exogenous factor, such as the background of radioactivity, does not adequately explain the phenomenon of increasing lung cancer rate over a short time. Atmospheric

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Table 7 RELATIVE RISKS (ODDS RATIOS) FOR SMOKING AND COAL FUMES EXPOSURE AMONG LUNG CANCER DEATHS (1985)

	Male		Female	
	O R	P-Value	O R	P-Value
Smoking	3.8	<0.01	1.90	<0.05
Coal fumes exposure	0.99		14.52	<0.001
Smok+non-smok+coal exp.+non-coal exp.	1.00		1.00	
Non-smok+non-coal exp.	0.31		0.31	
Smoking+non-coal exp.	4.40	<0.01	0.60	
Non-smoking+coal exp.	1.40		3.10	<0.05
Smoking+coal exp.	4.20	<0.01	5.80	<0.01

pollution accompanying industrialization might be the important factors for lung cancer, however the relationship between indoor air quality and health is, after all, closer and more direct than that between outdoor air quality and health.

If the indoor air pollution was the major relative etiologic factors for inducing woman lung cancer as demonstraled in our study, there are some phenomena still difficult to explain, for example, why did the incidence of woman lung cancer increased rapidly in recent years,and why the major cell type of woman lung cancer is adenocarcinoma and not epidermoid carcinoma, in general, the cell type induced by carcinogen B(a)P is mainly epidermoid carcinoma.

CONCLUSIONS & RECOMMENDATIONS

In Guangzhou, indoor air pollution was higher than outdoor, the main source was coal burning for domestic cooking, coal burning caused severe indoor air pollution not only, but also resulting homemakers urine-B(a)P increased. The OR of coal fumes exposure for woman was as high as 14.5. However, this possible cause proposed by epidemiologic study need further identifying by laboratory research.

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REFERENCES

1.Andrew JC et al.(1985) Lung Cancer in Woman Cancer, 55:2986-2898

2.Ayiomamitis A et al. (1985) Secular trends in lung cancer morbidity in Canada for the period 1970-1980 Prsented at the 4th World Conference on Lung Cancer, p.62

3.Sammartino P et al (1985) Lung cancer in woman Ibid, p.129

4.Svensson C (1985) Indoor exposure to radon from the ground and bronchial cancer among woman Ibid, p.35

5.Zhao HW et al (1985) The etiology and epidemiology of farmer's lung cancer in Xianwei County Ibid, p.77

RISK ASSESSMENT IN THE SE
OF PRIORITIES ON CONTROL
IN THE PREVENTION OF CHRO
RESPIRATORY DISEASES

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China

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Shanghai is an indus
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and sulfur dioxide (SO2)
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Chronic respiratory
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in all causes of deaths,
being cardiovascular dise
mortality rate of CRD is
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It is now well estab
important risk factor in
pulmonary diseases (COPD)
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Abstracts from The Second Annual Meeting of The International Society For Environmental Epidemiology. Part I.

Berkeley, California: August 13–15, 1990

CASE-CONTROL STUDY OF CHILDHOOD LEUKEMIA AND LYMPHOMA NEAR THE SELLAFIELD NUCLEAR PLANT

MJ Gardner, MP Snee, AJ Hall, S Downes, CA Powell, JD Terrell

This study examined excess incidence of childhood leukemia and lymphoma in children who lived near the Sellafield nuclear plant. The authors sought to determine if this excess was associated with established risk factors or with factors related to the plant or proximity to it.

A case-control study included 52 cases of leukemia, 22 cases of non-Hodgkin's lymphoma, and 23 cases of Hodgkin's disease. Cases were under the age of 25 y, had been born in the area, and had been diagnosed in the area from 1950 to 1985. A total of 1 001 controls taken from the same birth registers in which the cases were entered were selected. Data on antenatal abdominal x-rays, viral infections, behavioral factors, residential and occupational histories (including radiation dosimetry, etc.) were obtained from (a) medical records, (b) questionnaires to parents, and (c) linkage to Sellafield employment records.

To date, analysis has revealed that data quality is good. Concordance from duplicate sources, where available, is reasonably high with no indications of bias between cases and controls. Major analysis of the geographical distributions and potential explanations in terms of radiation exposure from the plant (e.g., ingestion of seafood, playing on the beaches, or parental employment) is currently underway and will be completed in the spring.

LUNG CANCER RISKS OF RESIDENTIAL RADON EXPOSURE IN NEW JERSEY

JB Schoenberg, JB Klotz, HB Wilcox

Government and private sector activities to reduce residential radon exposure are primarily based on extrapolation of data on lung cancer risk from the underground mine to the home setting. In 1985, the New Jersey Department of Health extended a previously conducted, statewide, population-based case control study of lung cancer in women to include radon measurements in former homes of the subjects. The principal objective was to determine if a lung cancer risk consistent with the mining study would be observed in this population.

The study extension collected year-long living-area radon exposure data in one residence for each of 433 histologically confirmed lung cancer cases and 402 controls. Previously, data on smoking, occupation, and diet had been collected for 994 cases and 995 controls. The criterion for inclusion was occupancy of a single residence for at least 10 y during the 10 to 30-y period that preceded ascertainment of cases or selection of controls.

Despite the few subjects who had high exposures and the gaps in exposure histories, a significant trend ($p = .04$) for lung cancer risk and exposure intensity was found, as was a slightly weaker trend ($p = .09$) for cumulative exposure. Further, the calculated relative risk coefficient per cumulative exposure unit (3.4% per WLM) was generally consistent with those of the underground miner studies. There was an inconsistent pattern of radon interaction with smoking.

Although the findings must be viewed cautiously, they support the current public health policy of assuming that the unit risks of radon documented for male miners also apply to lower exposures in the general population.

RADIATION AND MORTALITY AMONG WORKERS AT THE OAK RIDGE NATIONAL LABORATORY: FOLLOW-UP THROUGH 1984

S Wing, CM Shy, J Watson, S Wolf, J Wood, D Cragle, E Frome

A cohort of white male workers ($N = 8\,318$) employed at a Department of Energy research and development facility for more than 30 d between 1943 and 1972 was followed through 1984. There were 1 524 deaths and a loss to follow up of 8%. Estimates of exposure to penetrating external radiation were available from individual badges for 95% of working years; doses were estimated from nearby doses in years for which there were no data. Cumulative external dose was less than 10 mSv for 6 042 workers and greater than 50 mSv for 638 workers. A total of 3 740 workers were monitored for internal radiation exposure at some time during their employment at the plant.

The standardized mortality ratio (SMR) was 0.7 for all causes and 0.8 for all cancers. Leukemia SMRs were 1.6 (28 observed) for the total group and 2.2 (16 observed) among the subgroup that also had been monitored for internal exposure. No other cancer SMRs were significantly elevated. Excess leukemia mortality occurred after 1960 among workers hired prior to 1960. Standardized rate ratios (SRRs) using multiple-cause-of-death data, adjusted for age and calendar year, were calculated with the total population as the referent. Leukemia SRRs in the < 10, 10 to 50, and 50+ mSv groups were 0.8 (15 deaths), 1.6 (13 deaths), and 0.6 (2 deaths), respectively, with a 2 y exposure lag. Leukemia SRRs, excluding chronic lymphocytic leukemia, showed a similar pattern. Work in progress estimating dose-response relationships for leukemia and other cancer sites based on time-dependent lifetable regression models, adjusting for active worker status and other co-variates, will be presented.

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EFFECTS ON EARLY CHILDHOOD DEVELOPMENT OF PRENATAL EXPOSURE TO METHYLMERCURY

T Kjellström

A follow-up study of the developmental and psychological effects of prenatal exposure to methylmercury via fish was conducted in a group of New Zealand children whose mothers had a high fish consumption during pregnancy. Preliminary studies showed that fish with elevated mercury levels were sold in Auckland shops, and people who consumed substantial amounts of fish could reach intakes of mercury 3–4 times the WHO/FAO provisional tolerable weekly intake.

Mercury analysis of maternal hair identified 74 children with average prenatal exposure above 6 mg Hg/kg hair. These children were matched with three reference groups with lower exposures, and their performances in scholastic, psychological, and behavioral tests were compared.

The main findings were than (1) the "normal" results of the psychological test variables were influenced by the child's ethnic background and social class, (2) there is an apparent consistent association between high prenatal methylmercury exposure and decreased performance in the tests, (3) methylmercury exposure contributes only a small part of the variations in test results, and (4) an average hair mercury level during pregnancy of 13–15 mg Hg/kg hair was associated with the decreased test performance.

For the children who were tested both at age 4 y and age 6 y, there was a tendency for an association between the results of the Denver test at age 4 y and the Wechsler IQ at age 6 y. This indicates that the effects on the child's development and mental functions may be enduring.

LOOKING FOR TROUBLE: A CLINICAL PERSPECTIVE FOR FOCUS IN ENVIRONMENTAL EPIDEMIOLOGY IN THE 1990s

BW Case

Much has been written about the need for better exposure assessment, disease definition, statistical prowess, and "biologic rationale" in the conduct of environmental epidemiology. Not as much thought has been given to temporal trends in each of these very separate disciplines and their separate and combined effects on our knowledge of the environmentally diseased man, woman or child. Historically, epidemiology took the form of the classic detective story: the body on the floor (or in the hospital bed); the clue (exposure surrogate? disease? biomarker?) leading to the criminal (common source) who was quickly dispatched (prevention!). Unfortunately, the clues in our science have overwhelmed the crimes: in the process, we may lose our focus on the patient. Instrumentation and detection limits have made exposure assessment and its biologic surrogates far more accurate than exposure "reconstruction" pretends to be. Our understanding of disease (both definition and cause) have improved apace, yet we continue to rely on outmoded (ICD) codes and imperfect, nonspecific, and often biologically questionable "biomarkers." Most particularly, statistical analysis (and "risk assessment") have advanced to the point where a data set, if large enough and having enough covariates, may threaten to engulf the most intrepid investigator for years in what should have been a test of one null hypothesis. Even when this temptation is avoided, the effects of heterogeneity (genetic or otherwise) are dealt with inadequately, and potential confounders are unknown, much less accounted for. Biologic rationale is usually given token attention; besides, it can always be found before or after the fact (study) if we look long and hard enough. The result: a confused public, a welter of litigation, a plethora of artificially created problems, and exponentially increasing choices for *what to study* in an era of decreasing real funding. In this presentation, the following devil's advocacies are made. (1) Environmental epidemiology is a branch of clinical medicine. (2) As such, it should "do no harm," and it has the potential to do harm, e.g., in one location *preventing* fluoridation of water, in many instances undermining confidence in adequate nutrition and other public health measures, and even in one instance threatening lives on a grand scale in underdeveloped countries. (3) Accurate measurement is no substitute for accurate clinical thinking as to what, why, and whom to measure. (4) The *sine qua non* of choice must be not fundability, fashion, or flow charts: it must be clinical relevance. The importance of lead, cigarette smoke, and "clean air" will be used as examples, with converse examples being (non-amphibole) asbestos, some manmade mineral fibers, and selected environmental chemical exposures.

CLINICAL MANIFESTATIONS OF EOSINOPHILIA-MYALGIA SYNDROME

K Waller, D Hatch, T Saunders, L Goldman

Eosinophilia-myalgia syndrome (EMS) is a recently described illness associated with the use of supplemental L-tryptophan (L-T). The illness is characterized by unexplained peripheral eosinophilia (> 1 000 cells/mm³) and disabling myalgia, but the full range of clinical manifestations of EMS has not yet been described. As of February 8, 1990, 236 EMS cases have been reported to the California Department of Health Services (CDHS); 4 of these patients have died. This report summarizes clinical features and laboratory findings in 118 EMS patients for whom completed case report forms were available. The majority of cases were white middle-aged females; 87% of patients became ill during or after July 1989. Twenty-nine percent had been hospitalized. Symptoms reported by more than half of the patients included arthralgia (69%), dyspnea or cough (64%), rash (64%), and edema (51%). Pulmonary infiltrates were found in 16% of patients who received chest radiographs. Neuropathy had been diagnosed in 14% of patients; 3 have progressed to quadraparesis. Cardiac complications were reported in 6 patients. All patients reported use of L-T supplements prior to onset of illness; there was no clear relationship between dose or length of L-T use and severity of symptoms. EMS is a multisystemic illness that may have serious sequelae in some patients.

IMMUNOHISTOLOGICAL STUDY OF AFLATOXIN B_1, HEPATITIS B VIRUS AND HEPATOCELLULAR CARCINOMA

YJ Zhang, CS Lee, CY Yang, SN Lu, LL Hsieh, SL You, WL Wang, CJ Chen, RM Santella

The extraordinarily high hepatocellular carcinoma (HCC) mortality in Taiwan has been attributed to chronic hepatitis B virus (HBV) infection. However, epidemiologic studies have also suggested the importance of other environmental factors in the development of HCC. This immunohistological study examined the association of HCC with aflatoxins and HBV. Surgically removed and needle-biopsied HCC tissues and adjacent normal liver tissues were obtained from HCC patients in Taiwan and United States. An immunofluorescence method in which antibodies generated against the imidazole ring-opened form of major N7 guanine adducts of aflatoxin B_1 was used for the detection of aflatoxin-DNA adducts in these tissues. A peroxidase-antiperoxidase method that uses commercial kits (Biogenex Laboratories, Dublin, California) was employed for the detection of HBV surface antigen (HBsAg) in frozen tissue sections. Approximately 10% of HCC tissues from patients in Taiwan had detectable aflatoxin B_1 adducts, but the adduct was not detected in any HCC tissue obtained from patients in the United States. The HBsAg was detected in tumor tissues of 44.4% HCC patients and in adjacent normal tissues of 71.4% HCC patients from Taiwan, but none of the tumor or adjacent normal tissues from HCC patients in the United States was positive for HBsAg. Albumin adducts of aflatoxin B_1 in HCC patients and matched controls are also being carried out. The relative importance of these findings will be discussed.

AN EPIDEMIOLOGICAL STUDY OF LUNG CANCER IN XUAN WEI COUNTY, CHINA: CURRENT PROGRESS (I)

X He, W Chen, Z Liu, RS Chapman

In Xuan Wei County, Yunnan Province, lung cancer mortality rates are among China's highest in males and females. Previous studies have shown a strong association of lung cancer mortality with air pollution from "smoking" coal combustion. In the present quantitative risk assessment of indoor air pollution, this study shows a strong, obvious, on-site exposure-response relationship between Benzo(a)pyrene concentration in indoor air and lung cancer mortality. The results of this study strongly suggest the hypothesis that the indoor air pollution is the main risk factor for inducing lung cancer in Xuan Wei County. In the present case-control study, 100 newly diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence, which provided matching with respect to fuel use. Data from males and females were analyzed by conditional logistic regression. The results show that the presence of lung cancer in females who do not smoke is statistically significantly associated (at alpha = .05) with chronic bronchitis and family history of lung cancer. The results also suggest an association of lung cancer with duration of cooking food but not with passive smoking. The presence of lung cancer in males is

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associated with smoking, chronic bronchitis, family history of lung cancer, and personal history of cooking food. Effects of smoking and bronchitis in males are independent. Our studies suggest that lung cancer in Xuan Wei may occur through more than one mechanism of production. An etiologic study of lung cancer in nonsmokers is now in progress in Xuan Wei County, China.

EFFECTS OF OZONE ON LUNG FUNCTION IN CHILDREN LIVING IN THE NETHERLANDS

B Brunekreef, E Lebert, G Hoek, A van Kessel

In the Netherlands, a study is being conducted to investigate the temporal relationship between air pollution and lung function in school children. Several pollutants are measured continuously, among which are sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), airborne particulate (PM_{10}), and acid aerosols. Lung function is measured at the schools (mostly during the morning hours) at intervals from 1–3 wk, with more frequent measurements when pollutant levels are (expected to be) high.

During May and June 1989, relatively high levels of O_3 were observed in the Netherlands. On several days, 1-h maximum levels were between 200 and 240 $\mu g/m^3$, and 8-h maximum levels were between 160 and 200 $\mu g/m^3$.

About 500 children were studied during this period, and for each child a regression analysis was used to relate lung function to various measures of O_3 exposure. All analyses were linearly adjusted for the day of the year to correct for temporal trends in the data resulting from growth, learning effects, or motivational effects.

Only for PEF was the median of the estimated regression coefficients found to be significantly different from zero, with an estimated decrease of PEF of 5% at a 1-h maximum O_3 level (as measured on the day preceding the lung function tests) of 200 $\mu g/m^3$. FVC, $FEV_{1.0}$, and MMEF were not associated with exposure to O_3.

ARSENIC AND CADMIUM EXPOSURE IN CHILDREN LIVING NEAR TO BOTH ZINC AND COPPER SMELTERS

F Diaz-Barriga, MA Santos, L Batres, JJ Mejia, G Galvan, L Yanez, R Villalobos, M Zanatta, JL Medina, L Carrizales, H Hernandez, E Llamas

Exposure to both arsenic and cadmium is a common occurrence in San Luis Potosi City, Mexico. Two of the biggest smelters in Mexico are close to the City. One smelter produces approximately 8 500 tons of arsenic trioxide annually, and the other smelter produces about 700 tons of cadmium annually.

In this study, arsenic and cadmium levels were determined simultaneously in multiple environmental media and also from children's (3–6 y of age) urine. Two urban and one rural zone, respectively, were included: (1) Morales, which was within 2 km of the smelters; (2) Graciano, located 7 km from the smelters; and (3) Mexq, a rural community distanced 25 km from the smelters. Environmental media that was sampled included air, soil, household dust, and tap water.

Results of this investigation showed increased environmental cadmium levels close to the smelters for only soil, dust and, in some samples, air. Cadmium levels in urine samples collected from children who lived in the three areas did not differ. There were significantly higher levels of arsenic in tap water from the urban zones. The same relationship held for arsenic levels in soil and dust. (The air samples are being processed; therefore, results are not yet available.) Finally, increased systematic absorption of arsenic, as evidenced by urine arsenic levels, was clearly noted in children who lived near the smelters. The results obtained from questionnaires that were completed by mothers and teachers showed significant differences in intellectual performance and incidence of respiratory disease (confirmed by clinical examination) between children residing in urban and rural areas.

(This study was supported by the International Development Research Centre, Ottawa, Canada (3-P-87-0292); CONACYT (PCSACNA 051879); and SEDUE Federal.)

CONSEQUENCES OF AGENT ORANGE ON HEALTH: THE INSERM STUDY IN VIETNAM

INSERM North-South Network for Environmental Epidemiology in Vietnam*

The INSERM North-South Network* for Environmental Epidemiology in Vietnam is presently conducting three studies regarding exposure to herbicides during war and (a) non-Hodgkin's lymphoma, (b) primary carcinoma of the liver, and (c) molar pregnancy and choriocarcinoma. The three case-control studies consist of 100 cases and 100 controls for each pathology, matched by sex, age, and residency. Known confounders are assessed, e.g., (1) professional and other environmental exposures (all studies), (2) HBV infection and aflatoxins (study b), (3) reproductive history and nutritional status (study c). Exposure is assessed by a blind interview on past residency and war affectations, correlated with the US HERBS TAPE, and blood sampling for future measurements of 2,3,7,8-tetrachlorodibenzodioxin. To date, a French team has spent a total of 6 mo in Vietnam.

The feasibility of the three case-control studies will be discussed at the meeting. Epidemiologic investigations of dioxin exposure in Vietnam are actually feasible and cost-effective.

[*Members of the Network: L Abenhaim (formerly INSERM, presently McGill Univ., Montreal); S Cordier (INSERM U170); Cao Dai Le (Fac. Medicine, Hanoi, Vietnam); D Bard (INSERM Network); Dinh Cau Hoang (Hanoi); B Larouze (INSERM U13); and MF Gonnord (CNRS, Palaiseau, France).]

A FOLLOW-UP STUDY OF THE COMMUNITY NEAR THE McCOLL WASTE DISPOSAL SITE

JA Lipscomb, L Goldman, K Satin, D Smith, W Vance, R Neutra

In this study, the effect of interim clean-up measures on the current health of a community was investigated. We conducted a follow-up survey of 193 residents who lived near the McColl waste disposal site and near a nearby comparison area. Results from this survey were compared with results from a similar survey conducted 7 y earlier. Odors were detected at least once per week by 32.7% of "highly exposed" respondents in 1988 compared with 68.5% in 1981. However, prevalence odds ratios (PORs) that compared reporting of symptoms by residents in these two areas were greater than that of the 1981 survey for 89% of the symptoms. The PORs that compared reporting of symptoms between these two areas were greater than 2.0 for 64% of symptoms assessed in the current survey. Symptoms reported in excess did not represent a single organ or system or suggest a mechanism of response. The PORs that compared respondents who were very worried about the environment and those reporting no worry were greater than 2.0 for 86% of symptoms. These findings and environmental data from the area suggest that living in the McColl area and being very worried about the environment, rather than a toxicologic effect of chemicals from the site, explain the excess reported symptoms observed in this follow-up study.

SYMPTOM PREVALENCE AND ODOR-WORRY INTERACTION NEAR HAZARDOUS WASTE SITES

D Shusterman, J Lipscomb, R Neutra, K Satin

Retrospective symptom prevalence data collected from more than 2 000 adult respondents who lived near three different hazardous waste sites were analyzed with respect to both self-reported "environmental worry" and frequency of smelling environmental—particularly petrochemical—odors. Significant positive relationships were observed between the prevalence of several symptoms (e.g., headache, nausea, eye and throat irritation) and both frequency of odor perception and degree of worry. Headache, for example, showed a prevalence odds ratio of 5.0 for respondents who reported smelling environmental odors frequently vs. those smelling no such odors, and 10.8 for those who described themselves as "very worried" vs. "not worried" about environmental conditions in their neighborhood. Elimination of respondents who ascribed their environmental worry to illness in themselves or in family members did not materially affect the strength of the observed associations (corrected prevalence odds ratios 5.6 and 11.1, respectively). In addition to their independent effects, odor perception and environmental worry exhibited positive interaction as determinants of symptom prevalence, as evidenced by a prevalence odds ratio of 38.1 for headache among the high-worry/frequent-odor group vs. the no-worry/no-odor group. In comparison for neighborhoods with no nearby waste sites, environmental worry was also associated with symptom occurrence. Potential explanations for these observations are presented, including the possibility that odors serve as a sensory cue for the manifestation of stress-related illness among individuals who are concerned about the quality of their neighborhood environment.

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Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China

ZHIYUAN LIU*†, XINGZHOU HE* AND ROBERT S CHAPMAN**

Liu Z (Institute of Environmental Health and Engineering, Chinese Academy of Preventive Medicine, 29 Nan Wei Road, Beijing 10050, China), He X and Chapman R S. Smoking and other risk factors for lung cancer in Xuanwei, China. *International Journal of Epidemiology* 1991; 20: 26–31.

In Xuanwei County, Yunnan Province, lung cancer mortality rates are among the highest in China in both males and females. Previous studies have shown a strong association of lung cancer mortality with indoor air pollution from 'smoky' coal combustion. In the present case-control study, 110 newly-diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence (which provided matching with respect to fuel use). This design allowed assessment of known and suspected lung cancer risk factors other than those mentioned above. Data from males and females were analysed by conditional logistic regression. In females who do not smoke, the presence of lung cancer was statistically significantly associated with chronic bronchitis (odds ratio [OR] = 7.37, 95% confidence interval [CI]: 2.40–22.66) and family history of lung cancer (OR 4.18, 95% CI: 1.61–10.85). Females' results also suggested an association of lung cancer with duration of cooking food (OR 1.00, 9.18 and 14.70), but not with passive smoking (OR 0.77, 95% CI: 0.30–1.96). In males, lung cancer was significantly associated with chronic bronchitis (OR 7.32, 95% CI: 2.66–20.18), family history of lung cancer (OR 3.79, 95% CI: 1.70–8.42), and personal history of cooking food (OR 3.36, 95% CI: 1.27–8.88). In males a dose-response relationship of lung cancer with smoking index (years of smoking*amount of smoking) was shown by risks of 1.00, 2.61, 2.17 and 4.77.

Examination of Chinese nationwide cancer mortality statistics reveals that lung cancer mortality rates in Xuanwei County, Yunnan Province, are among the highest in China.[1] From 1973 through 1975, annualized male lung cancer death rates, age-adjusted to the 1964 China population, were 27.7 and 6.8 per 100 000 in Xuanwei and China, respectively. Corresponding mortalities in females were 25.3 and 3.2 per 100 000. Marked geographical variation in lung cancer mortality exists within Xuanwei. The county can be divided into high-, medium- and low-mortality areas, in which age-adjusted lung cancer mortalities in both sexes are 126.1, 20.9 and 6.0 per 100 000, respectively.

Xuanwei residents have traditionally burned three types of fuel, 'smoky' coal, 'smokeless' coal, and wood, for residential heating and cooking. Until the 1980s fuel was nearly always burned in an open, unventilated fire pit in the floor of the dwelling's main room; such fire pits are still widely used, though the use of ventilated stoves is increasing. Women have generally been responsible for starting and tending the domestic fire and cooking food, though men assume these responsibilities in some families.

Tobacco smoking is very rare in Xuanwei women, yet women's lung cancer rates are comparable to men's. Also, a survey of past fuel use showed that in the high-, medium- and low-mortality areas of Xuanwei, the percentages of families using smoky coal before 1958 were 87.6%, 60.1% and 6.1% respectively. Corresponding percentages of families using wood were 1.4%, 19.9% and 67.1%. Indoor concentrations of benzo(a)pyrene (BAP) averaged 627 ug/100 metres^3 (m^3) in the high-mortality area, and 46 ug/100 m^3 in the low-mortality area. In addition indoor pollution samples from the high-mortality area exhibited higher Ames-test mutagenicity than those from the low-mortality area.[2,3] All of these observations have served to suggest an association between indoor smoky coal burning and lung cancer in Xuanwei.

The case-control study reported here was designed to supplement existing information by assessing the influence of factors other than fuel type on the occurrence of lung cancer in Xuanwei. Such factors, includ-

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ing tobacco smoking, family history of lung cancer, history of chronic bronchitis, and cooking habits, have been associated with lung cancer in areas other than Xuanwei, but their importance as contributors to lung cancer in Xuanwei has not yet been systematically determined. The present study also allowed comparison of the relative impact of these factors in males and females.

MATERIALS AND METHODS

In Xuanwei, 93.4% of the total population were farmers in 1982. Because of this, and because lung cancer mortality in Xuanwei farmers is high,[2] this study was confined to farmers. Concentrating the target population tended to increase the validity of the findings.[4] Between November 1985 and December 1986, we identified 112 cases of newly-diagnosed lung cancer at Xuanwei hospitals and clinics. After exclusion of two patients with unknown addresses, 110 lung cancer patients (56 males and 54 females) were included in data analysis. Of these, 19 (17%) had been diagnosed on the basis of cytological/pathological findings, and the remainder on the basis of clinical histories and X-rays.

Controls were selected to match lung cancer patients with respect to age (±2 years), sex, and village of residence. Because fuel use habits and dwelling types are similar within individual Xuanwei villages, this design was expected to provide effective matching with respect to indoor fuel type and dwelling type.

Such matching was sought because it would increase the effectiveness with which factors other than fuel type could be assessed. Cases and controls were matched on village, with as many eligible controls included as possible. Therefore, we selected more controls for each case in a large village than in a small village. The numbers of controls per case varied from one to five. After exclusion of 26 controls because of erroneous questionnaire responses, 426 controls were included in data analysis, an average of 3.87 controls per case. There were 9 cases with 1 control, 15 cases with 2 controls, 15 with 3 controls, 13 with 4 controls, and 58 with 5 controls.

A standardized questionnaire of the closed-question type was developed. Study factors included tobacco use history, family and personal medical history, domestic fuel use history, indoor fuel use history, personal history of cooking food, dwelling type, ethnic group (nationality), and socioeconomic and educational levels. After strict interviewer training and field testing, this questionnaire was administered directly to all lung cancer patients and controls. No interviewer or study subject knew the purpose of the study and hypotheses.

A summary index of tobacco smoking was developed for each subject. The smoking index was calculated by multiplying the duration of smoking (in years) by the amount of tobacco smoked (in kilograms per month). A subject was considered to have a positive family history of lung cancer if at least one relative was reported to have had the disease. The relatives included subjects' parents, siblings and children, and parents' siblings. A subject was considered to have a positive history of chronic bronchitis if he or she had been diagnosed by a doctor to have this condition, or reported cough for at least three months per year for at least two years before the year of interview. A female subject was considered to have been exposed to passive smoking if there was at least one smoker (mainly husband) who lived in the same household.

To assess the effects of individual independent variables, unmatched, unadjusted odds ratios (ORs) were calculated.[5] Confidence intervals were calculated using Miettinen's method.[6] Dose-response relationships were examined for variables related to smoking and cooking. Trends within these relationships were tested by extension of the Mantel-Haenszel procedure.[7]

To develop adjusted estimates of ORs associated with selected factors and interactions, conditional logistic regression models were also constructed for males and females.[8] In these models, all variables were dichotomous, assuming values of 0 or 1. The selected risk factors and interactions were treated as independent variables, and the presence or absence of lung cancer was treated as the dependent variable. These analyses were performed using the PECAN program.[9,10]

RESULTS

Distributions of characteristics in cases and controls are presented by gender in Table 1. Age, family size, ethnic group, birthplace, educational level, and dwelling type were comparable in cases and controls, so these factors were not considered further in data analysis. The effect of active tobacco smoking was not evaluated in females, since only one female (a control subject) had ever smoked tobacco. The village matching provided effective matching on fuel type because fuel-use habits (type and average amount) were similar in cases and controls.

Crude and adjusted ORs for smoking and cooking habits are presented with 95% confidence intervals for males in Table 2. No relationship between lung cancer and ever having smoked was observed. There was a suggestion of monotonic dose-response relationships of lung cancer with the age at which smoking began, duration of smoking and amount smoked by month.

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TABLE 1 *Comparison of lung cancer cases and controls, Xuanwei, China, 1985–1986*

Factor	Males		Females	
	Cases	Controls	Cases	Controls
Average age (years)	52	50	52	52
No. of people in family now	5.6	5.4	5.6	5.4
No. of people in family 20 years ago	5.8	5.5	5.9	5.5
Han nationality (%)	94.6	96.9	98.2	97.0
Born in Xuanwei (%)	100	100	100	98.0
Two-storey dwelling (%)	98.2	99.1	100	100
Amount of 'smoky' coal burnt (tons/year)	4.2	4.2	4.0	4.1
Amount of wood burnt (tons/year)	0.8	0.9	0.8	1.0

TABLE 2 *Odds ratios (OR) and 95% confidence intervals (CI) for lung cancer in males according to smoking and cooking, Xuanwei, China, 1985–1986*

Factor	Cases	Controls	ORc*	ORa**	95% CI
Ever-smoker					
No	4	19	1.00	1.00	
Yes	52	205	1.20	1.26	0.30– 5.26
Age of starting to smoke (years)					
Never	4	19	1.00	1.00	
>20	20	80	1.19	1.10	0.25– 4.93
⩽20	32	125	1.22	1.39	0.32– 6.06
Trend (p value)			(p>0.05)		
Years of smoking					
0	4	19	1.00	1.00	
<35	30	146	0.98	1.07	0.25– 4.59
⩾35	22	59	1.77	1.71	0.36– 8.12
Trend (p value)			(p>0.05)		
Amount of smoking (kg/per month)					
Never	4	19	1.00	1.00	
⩽0.5	25	93	1.28	1.41	0.33– 6.09
0.6–1.0	20	93	1.02	1.09	0.24– 4.82
>1.0	7	19	1.75	1.91	0.32–11.40
Trend (p value)			(p>0.05)		
Smoking index†					
<2	4	30	1.00	1.00	
2–	24	99	1.82	2.61	0.69– 9.82
20–	16	74	1.62	2.17	0.55– 8.64
35–	12	21	4.28	4.70	1.03–21.40
Trend (p value)			(p<0.05)		
Often cooks food					
No	44	200	1.00	1.00	
Yes	12	24	2.27	3.36	1.27– 8.88

*ORc = Crude odds ratio.
**ORa = Odds ratio after adjustment by conditional logistic regression for other risk factors.
†Smoking index = Years of Smoking*Amount of smoking.

However, none of these relationships was statistically significant. In contrast, a statistically significant dose-response relationship of lung cancer with smoking index was observed. The adjusted OR in men who often cooked food (at least once a day) was 3.36 (95% CI: 1.27–8.88). The adjusted ORs were slightly larger than the crude ORs.

Crude and adjusted ORs for cooking and passive smoking are presented for females in Table 3. No dose-response relationship of lung cancer with age at which the woman began to cook food was observed, but the OR associated with the age at which the woman began to cook food (11–15 years old) was significant. Adjusted ORs associated with the duration of cooking were much larger than crude ORs. There was a suggestion of dose-response relationship of lung cancer with the duration of cooking food for the adjusted ORs. No relationship of lung cancer with passive smoking was observed.

Odds ratios for family history of lung cancer and personal history of chronic bronchitis were significantly associated with lung cancer in both sexes but duration of using an unventilated fire pit was not (Table 4). All conditional logistic regression ORs were larger than crude ORs in Table 4.

DISCUSSION

This study was intended to supplement previous studies which had shown a strong association of indoor smoky coal combustion with lung cancer in Xuanwei County.[2,3] Full understanding of lung cancer aetiology in Xuanwei, and comprehensive risk assessment of the effect of smoky coal use, require systematic assessment

TABLE 3 *Odds Ratios (OR) and 95% confidence intervals (CI) for lung cancer in females according to cooking and passive smoking, Xuanwei, China, 1985–1986*

Factor	Cases	Controls	ORc*	ORa**	95% CI
Age of starting to cook					
>15	13	73	1.00	1.00	
11–15	30	69	2.44	2.37	1.09– 5.15
⩽10	11	60	1.03	1.25	0.45– 3.49
Trend (p value)			(p>0.05)		
Years of cooking					
⩽30	7	53	1.00	1.00	
31–44	28	85	2.49	5.18	1.76– 47.49
⩾45	19	64	2.25	14.70	1.61–134.03
Trend (p value)			(p>0.05)		
Passive smoking					
No	9	26	1.00	1.00	
Yes	45	176	0.74	0.77	0.30– 1.96

*ORc = Crude odds ratio.
**ORa = Odds ratio after adjustment by conditional logistic regression for other risk factors.

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TABLE 4 *Adjusted odds ratios (OR) and 95% confidence intervals (CI) for lung cancer in males and females, according to familial history of lung cancer, history of chronic bronchitis and years using unventilated fire pit, Xuanwei, China, 1985–1986*

Factor	Males			Females			Total		
	Case	Control	ORa* (95% CI)	Case	Control	ORa (95% CI)	Case	Control	ORa (95% CI)
Familial history of lung cancer									
No	41	200		45	192		86	392	
Yes	15	24	3.79 (1.70–8.42)	9	10	4.18 (1.61–10.85)	24	34	3.75 (2.05–6.83)
History of chronic bronchitis									
No	39	209		38	184		77	393	
Yes	17	15	7.32 (2.66–20.18)	16	18	7.37 (2.40–22.66)	33	33	7.61 (3.62–16.00)
Years using unventilated fire pit									
<45	22	107		21	84		43	191	
≥45	34	117	1.78 (0.46–6.93)	33	118	0.73 (0.20–2.60)	67	235	1.12 (0.46–2.74)

*ORa = Odds ratio after adjustment by conditional logistic regression for other risk factors.

not only of fuel use, but of other known and suspected risk factors as well. To achieve such an assessment, we chose a study design which provided effective case-control matching with respect to fuel type and average amount used as well as to age and gender.

Xuanwei is a very rural area. In the present study, almost all lung cancer patients were diagnosed by the county hospitals. Only 17% of the lung cancer cases were based on cytological/pathological findings, 83% were based on clinical histories and X-ray findings. Therefore, misclassification of the cases may exist in the study. However, other reasons may improve validity of lung cancer diagnosis in the study. Because of poor medical care in Xuanwei, most lung cancer patients had reached an advanced stage of the disease when diagnosed, and local doctors had wide experience of this diagnosis because of the high lung cancer morbidity in Xuanwei. In order to assess validity of the diagnosis, we also followed up a number of lung cancer patients from the study, almost all of whom died within six months of diagnosis.

In both males and females, the current study disclosed consistent and statistically significant associations of lung cancer with chronic bronchitis and positive family history of lung cancer. Lung cancer was also associated with the frequency of cooking food (in males) and the duration of cooking food (in females), even after the matching on fuel type inherent in the study design. Not surprisingly, lung cancer was associated with active smoking in males. No association with passive smoking was observed in females.

In Xuanwei, women are generally responsible for cooking food, so the variable 'cooks or does not cook food' could not be assessed in females. However, the ORs associated with the variable 'years of cooking' suggested that lung cancer risk increased with increase in duration of cooking (Table 3). There was no dose-response relationship between lung cancer and age at which a woman began to cook food. This observation may be due to the possibility that women who reported cooking food at less than ten years old did not really cook food at that age. The OR in males who often cooked food was over three times greater than in those who did not. It is likely that those who cook food inhale more coal-smoke pollution than those who do not. Wu *et al* reported that subjects exposed to burning coal used for heating or cooking in a stove or fireplace during the majority of childhood and the teenage years had a lung cancer risk 2.3 times higher than subjects who were not so exposed.[11] Wang *et al* have reported similar results from China.[12] Gao *et al* reported increased risk of lung cancer in Shanghai women who cook frequently with rapeseed oil.[13] This observation raises the question of whether pollutants associated not only with the cooking fuel but also with the cooking method promote lung cancer.

The observed association of lung cancer with positive family history of the illness may be attributable in part to recall bias. However, our results are consistent with other studies[14–17] which tends to reinforce the validity of the association. Our relative risk estimates for positive family history of lung cancer, 3.79 in males and 4.18 in females, were also similar to previous studies. The association may be due partly to the fact that a subject's relatives lived in the same environment as the subject for some time. Mulvihill has postulated that some abnormal types of gene might increase sensitivity to environmental carcinogens.[18] Further research will be necessary to elucidate and distinguish the roles of genetic and environmental factors in carcinogenesis.

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Tobacco smoking is generally accepted to be a major cause of lung cancer.[19–22] We observed an association of lung cancer with tobacco smoking in males, and this observation tended to enhance confidence in the results. However, the association was weaker than has been reported in many previous studies.[13,19] When considered individually, duration of smoking, amount of smoking, and age at which smoking began were only weakly associated with the illness. Only the smoking index derived by multiplying duration by amount of smoking was significantly associated with lung cancer.

These observations may be due partly to the fact that only 23 (8.2%) of 280 males in this study were lifetime non-smokers. In such a small comparison group, even fairly small changes in the distribution of non-smokers between cases and controls could have produced marked differences in observed ORs associated with smoking. More importantly many farmers in Xuanwei smoke tobacco through a long bamboo cylinder partly filled with water and the passage of smoke through the water may filter out carcinogenic substances. Studies comparing the composition of water-filtered to unfiltered tobacco smoke are currently in progress.

It is also quite conceivable that the large amount of air pollutants inhaled during indoor smoky coal burning in Xuanwei partly overwhelm the carcinogenic effect of tobacco smoking. For example, as mentioned above, the average indoor concentration of BAP in the Xuanwei region of high lung cancer mortality was 627 ug/100 m^3 in a recent survey. An individual inhaling 12 m^3 of air per day might therefore inhale 9154 ug of BAP in a year if he or she spent eight hours per day indoors. In contrast, an individual smoking 20 cigarettes per day might be expected to inhale only about 700 ug of BAP in one year.[23] Thus, it is not especially surprising that the ORs associated with smoking in Xuanwei males were smaller than reported in other studies. Because unusual environmental conditions prevail in Xuanwei, it would not be advisable to generalize these ORs to other areas.

Smoking is very rare in Xuanwei females. In addition, we observed no association of lung cancer with passive smoking in females. Such an association has been reported in several previous investigations.[24–27] In non-smoking women in Shanghai, Gao *et al* observed a limited association of lung cancer with passive smoking; in that study the relative risk ranged from 1.0 in women living less than 20 years with a smoking husband to 1.7 in those living with a smoking husband for at least 40 years.[13] However Koo *et al* have not observed a consistent association of lung cancer with passive smoking in Chinese women.[28–30] These authors also stated that correlates of passive smoking such as diet and socioeconomic status can act as important confounders when the health risks of passive smoking are evaluated.[31] The heavy indoor air pollution in Xuanwei may also overwhelm the carcinogenic effect of passive smoking. The effect of passive smoking on lung cancer may depend on local environmental factors and results obtained in a given region may therefore not be applicable to other regions.

In summary, this study was undertaken to supplement existing evidence showing a strong association of lung cancer with indoor use of smoky coal in Xuanwei. Our results disclose important associations of lung cancer with factors other than fuel type and therefore indicate that these factors must be considered in any comprehensive, quantitative risk assessment of lung cancer in Xuanwei. Our results also confirm indirectly that smoky coal pollution is an important determinant of lung cancer in Xuanwei. A separate case-control study, which will allow simultaneous direct analysis of the effects of indoor air pollution and other known and suspected lung cancer risk factors in Xuanwei, is currently in progress.

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REFERENCES

1 Office of research of cancer prevention and treatment, Ministry of Health: *Data of cancer mortality in the People's Republic of China*, Beijing, 1980.

2 Mumford J L, He X Z, Chapman R S, *et al.* Lung cancer and indoor air pollution in Xuanwei, China. *Science* 1987; 235: 217–20.

3 Chapman R S, Mumford J L, Harris D B *et al.* The epidemiology of lung cancer in Xuanwei, China: Current progress, issues, and research strategies. *Arch Environ Health* 1988; 3: 180–5.

4 Schlesselman J J. *Case-control studies: Design, Conduct, Analysis.* New York. Oxford University Press, 1982.

5 Lilienfeld A M, Lilienfeld D. *Foundations of epidemiology.* New York. Oxford University Press, Second, 1980.

6 Miettinen O S. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976; 103: 226–35.

7 Mantel N. Chi square tests with one degree of freedom: extension of the Mantel-Haenszel procedure. *J Am Stat Assoc* 1963; 58: 690–700.

8 Breslow N E, Day N E. *Statistical methods in cancer research, Vol I, The analysis of case-control studies.* Lyon, IARC Scientific Publication No 32, 1980.

9 Gail M H, Lubin J H, Rubinstein L V. Likelihood calculations for matched case-control studies and survival studies with tied death times. *Biometrika* 1981; 68: 703–7.

10 Storer B E, Wacholder S, Breslow N E. Maximum likelihood fitting of general risk models to stratified data. *Appl Statist* 1983; 32: 172–81.

11 Wu A H, Henderson B E, Pike M C, Yu M C. Smoking and other risk factors for lung cancer in women. *JNCI* 1985; 74: 747–51.

12 Wang X Z. Lung cancer and air pollution indoor and outdoor. *Environment and Health* 1983; 1: 7–12.

13 Gao Y T, Blot W J, Zheng W, *et al.* Lung cancer among Chinese women. *Int J Cancer* 1987; 40: 604–9.

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Higginson J, Jenson O M. Epidemiological review of lung cancer in man. In: Mohr E, Schwachi D, Tomatis L (eds). *Air pollution and cancer in man*. Lyon, IARC, 1977.

Tokuhata G K, Lilienfeld A M. Familial aggregation of lung cancer in human. *JNCI* 1963; 30: 289–312.

Ooi W L, Elston R C, Chen V W, Bailey-Wilson J E, Rothschild H. Increased familial risk for lung cancer. *JNCI* 1986; 76: 217–22.

Goffman T E, Hassinger D D, Mulvihill J J. Familial respiratory tract cancer. *JAMA* 1982; 247: 1020–3.

Mulvihill J J. Host factors in human lung tumour: an example of ecogenetics in oncology. *JNCI* 1976; 53: 3–7.

Loeb L A, Ernster V L, Warner K E, Abbotts J, Laszlo J. Smoking and lung cancer: an overview. *Cancer Res* 1984; (12, pt 1): 5940–58.

Wynder E L, Graham E A. Tobacco smoking as a possible etiological factor in bronchogenic carcinoma. *JAMA* 1950; 143: 329–36.

Levin M L, Goldstein H, Gerhardt P R. Cancer and tobacco smoking: Preliminary report. *JAMA* 1950; 143: 336–8.

Doll R, Hill A B. Smoking and carcinoma of the lung: Preliminary report. *Br Med J* 1950; 2: 739–48.

WHO: *Health hazards of the human environment*. Geneva, 1972.

Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer* 1981; 27: 1–4.

Correa P, Pickle L W, Fontham E, Lin Y, Haenszel W. Passive smoking and lung cancer. *The Lancet* 1983; ii: 595–7.

Garfinkel L. Passive smoking and cancer—American experience. *Prev Med* 1984; 13: 691–7.

Blot W J, Fraumeni J F Jr. Passive smoking and lung cancer. *JNCI* 1986; 77: 993–1000.

Koo L C, Ho J H–C, Saw D. Active and passive smoking among female lung cancer patients and controls in Hong Kong. *J Exp Clin Cancer Res* 1983; 4: 367–75.

Koo L C, Ho J H–C, Saw D. Is passive smoking an added risk factor for lung cancer in Chinese women? *J Exp Clin Cancer Res* 1984; 3: 277–83.

Koo L C, Ho J H–C, Saw D, Ho C–Y. Measurement of passive smoking and estimates of risk for lung cancer among nonsmoking Chinese females. *Int J Cancer* 1987; 39: 162–7.

Koo L C, Ho J H–C, Rylander R. Life-history correlates of environmental tobacco smoke: A study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. *Soc Sci Med* 1988; 26: 751–60.

(Revised version received September 1990)

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Chinese J Prev Med 23(5):270-273, 1989.

Analysis of Risk Factors for Female Lung Adenocarcinoma in Haerbin: Indoor Air Pollution

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An investigation including a matched case control study and measurement of indoor air pollution, of risk factors for female lung adenocarcinoma in Haerbin showed that high coal consumption index (HCCI $OR=10.59$), indoor smog pollution in winter ($OR=15.19$) and low ceiling height of the living room ($OR=12.49$) were main risk factors for the cancer. It was further confirmed by the measurement that the mean daily measured concentrations of TSP and Bap in inhabitants' bedroom in winter were 4.4 and 26.7 times respectively as high as those of outdoor air concentrations. No significant association with cigarette smoking and indoor passive smoking was found.

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Non-author Translation

Analysis of Risk Factors for Female Lung Adenocarcinoma in Haerbin City------Indoor Air Pollution

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ABSTRACT:

KEY WORD: Lung Tumor, Adenocarcinome, Female, Air Pollution, Coal, Smog.

Some research has shown that pulmonary squamous carcinoma and pulmonary small cell carcinoma have a close relationship to cigarette smoking, but the pulmonary adenocarcinoma, especially in female, bears a little relation to cigarette smoking(1--3). Its main risk factor is still unknown. Pulmonary adenocarcinoma accounts for a large proportion in Chinese women(4). So, we investigate the risk factors for female pulmonary adenocarcinoma in Haerbin City. The research includes two aspects.

I. Case-contral Study of Female Pulmonary Adenocarcinoma in Haerbin.

MATERIALS and METHODS

1. Case, Item and Method:

This 1:1 matched-pair study was performed on fifty-five females, 30--69 years old, who had confirmed diagnosis of pulmonary adenocarcinoma between January 1985 to November 1986. All cases were residents of Haerbin City. The controls were randomly selected from female resident of Haerbin City with the same age (þ5 years).

The researchers surveyed the cases and controls with a uniform questionaire which included housing condition lasting more than three years after birth, history of using fuel, cooking, indoor smog pollution in winter (WISP), indoor and outdoor air pollution around the housing area, occupation, cigarette smoking and passive smoking (PS) and history of chronic pulmonary disease (CPD).

2. Statistical Method:

The latent period is usually more than 20 years when nonoccupational factors cause pulmonary carcinoma. Therefore we analysed the residential history data for the 10 years from 1955 to 1964. We calculate weighted mean if the subjects moved, screened out suspicious risk factors with χ^2_{MH} test and analyse the significant related factors with Conditional Logistic

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Regression Analysis. All calculations were done on an IBM PC/XT computer.

RESULT:

1. Test for matching: the cases and controls wrer matched for nationaly, marital status, education and the time of living in Haerbin City. (P>0.05)

2. The relationship between pollution of the housing micro-environment (HME) and pulmonary adenocarcinoma: A single factor analysis showed that there were significant difference in seven items which were sifted out from among twenty suspicious risk factors. Five items among them related to the pollution of HME with high OR value (Table 1)

Table 1. Significant Risk Factors of HME Pollution Related to Pulmonary Adenocarcinoma (Maximun Likelihood Method)

Variable	$\bar{X}$	OR	95% CI	P
X1 Coal Consumption Index (CCI)*	11.29	6.18	2.13--17.92	0.0005
X2 WISP	4.90	3.75	1.16--12.08	0.014
X3 Free Ventilation between Bedroom & Kitchen (FVBK)*	4.04	2.86	1.03--7.96	0.023
X4 Other Fuel Consumption*	2.97	2.38	0.89--6.35	0.043
X5 Low Ceiling Height (<2.5 M)	3.97	4.33	1.02--18.32	0.024
X6 PCD	2.76	2.57	0.84--7.84	0.049
X7 Noxious Occupational History	3.28	2.63	0.92--7.48	0.036

*Coal Consumption (kg) per year - Housing Area (M^2)=CCI
*FVBK=There is no seperation between bedroom and kitchen or warming and cooking in bedroom
*Other fuel refers to wood, straw and bark etc.

The above-mentioned seven items were fit by the Conditional Logistic Regression Model with the stepwise contrast technique. Three items [CCI (X1), WISP (X2) and Low ceiling of house (X5)] were in keeping with the model , and there was obvious synergistic action between them (Table 2).

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Table 2. Parameter Table of Conditional Logistic Regression Analysis Fit to Seven Items Related to Pulmanory Adenocarcinoma

Quantity of Parameter	Likelihood Function Logarithmic Value	ß Value and 95 % CI		
		X1	X2	X3
0	-38.12309			
1	31.63661	1.85 (0.48--3.22)		
2	-27.32787	2.17 (.78--3.56)	1.93 (.42--3.44)	
3	-23.5642	2.36 (.75--3.97)	2.72 (1.03--4.41)	2.56 (.09--5.03)

According to the relationship between OR and ß(5), OR value that were transformed from X1, X2 and X5 are 10.59, 11.59 and 12.49 respectively. This indicates that the pollution of HME plays an important role in the onset of female pulmanory adenocarcinoma in Haerbin City.

3. Other factors: The OR value for exposure to CPD and noxious occupational factors such as asbestos, polycyclic aromatic hydrocarbon (PAH) and Ni etc. in the onset of pulmanory adenocarcinoma are 2.57 and 2.63 respectively.

No significant difference in cigarette smoking and its index (daily quantity of smoking X quantity of smoking year), PS and PS index and other nine items were seen.

II. Determination of the Indoor Air Pollution:

This determination was to further understand the effect of indoor air pollution and the effect of high CCI and FVBK on indoor air pollution.

MATERIALS and METHODS

1. Purpose and sampling method: In order to understand the effect of CCI and FVBC on the pollution of indoor air, we used the factors influential in HME such as the height of room, amount of indoor cigarette smoking etc. as the matched-pair comparison factors, Thirteen families that warm their house by a coal stove were selected from the above-mentioned control group for this determination. They consisted of four families with a high CCI (including one family of FVBK) and nine families with a low CCI

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(including four families of FVBK and five families of non-FVBK).

KC-8301 dust sampler and "49-type" filter membrane were employed to collect samples in the bedroom continuously for seventy-two hours at a flow of 13 liter per minite.

2. Index and method of determination: The method of increasing weight in filter membrane was employed to measure the total suspended particulate (TSP) and inhalable particulate (IP). 3,4-benzopyrene (Bap) was determined by paper chromatography and fluorescent spectrophotometry(6).

Sampling was performed from December 1986 to January 1987. Related meteorological data was kindly provided by Meteorological Bureau of Haerbin City.

RESULT:

1. Indoor air pollution in Haerbin City in winter: The mean daily measured concentration of TSP in inhabitants' bedrooms in winter was as high as 0.67 mg/m . This is about 4 times higher than the Criterion of China Air Sanitation. IP that is more harmful to human account for 90 % of TSP and the concentration of Bap is about 26 times higher than recommended sanitary criterion (Table 3).

Table 3. Mean Daily Concentration of TSP, IP and Bap in Inhabitants' Bedroom in Winter

Sample No.	TSP(Mg/M^3)	IP(Mg/M^3)	IP/TSP (%)	Bap(ug/100 M^3)
1	1.03	0.88	85	5.05
2	0.99	0.88	89	4.42
3	0.86	0.81	94	5.86
4	0.82	0.71	87	5.11
5	0.75	0.71	94	5.98
6	0.67	0.55	82	3.99
7	0.67	0.60	90	2.50
8	0.59	0.54	92	1.29
9	0.58	0.54	93	2.26
10	0.53	0.46	86	2.03
11	0.52	0.45	86	2.03
12	0.42	0.39	93	2.67
13	0.42	0.39	93	1.06
Median	0.67	0.55	90	2.67

2. Analysis of factors related to indoor air pollution:

High CCI: The concentration of Bap and TSP in the bedroom in the families with high CCI is high as well. ($P<0.03$) (Table 4)

FVBK: When CCI is of the same level, the concentration of

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Bap in the bedroom of FVBK is higher than that in the bedroom of non-FVBK. It approaches the significant level (Table 5)

Table 4. Mean Daily Concentration of Bap and TSP under high and Low CCI condition

High CCI			Low CCI		
CCI ($kg/m^2/yr$)	TSP (mg/m^3)	Bap ($ug/100m^3$)	CCI ($kg/m^2/yr$)	TSP (mg/m^3)	Bap ($ug/100m^3$)
254	0.99	4.42	80	0.49	1.65
226	0.67	3.99	111	0.59	1.29
159	0.75	5.98	113	0.52	2.03
200	0.86	5.86	40	0.67	2.50
X1=0.82	X2=5.06		Y1=0.57	Y2=1.87	
t1=3.12	t2=5.64		P1=0.02	P2=0.0013	

Table 5. Mean Daily Concentration of Bap and TSP Under FVBK and Non-FVBK Condition

FVBK			Non-FVBK		
CCI ($kg/m^2/yr$)	TSP (mg/m^3)	Bap ($ug/100m^3$)	CCI ($kg/m^2/yr$)	TSP (mg/m^3)	Bap ($ug/100m^3$)
254	0.99	4.42	226	0.67	3.99
114	1.03	5.05	113	0.53	2.03
114	0.82	5.11	105	0.42	1.06
52	0.42	2.67	71	0.58	2.26
X1=0.82	X2=4.31		Y1=0.55	Y2=2.34	
t1=1.78	t2=2.37		P1=0.13	P2=0.056	

DISCUSSION

The relationship between indoor microenvironmental pollution and female pulmonary carcinoma is still an unsolved problem. About 90 % of human life is spent indoors. So, it is very important to study the effect of the quality of indoor micro-environment on health. In the northen city of China, coal is the main fuel (especially before the 1970s). People usually close windows during the long period of winter so that the smog produced by cooking, warming and cigarette smoking etc. is difficult to disperse. It causes serious pollution of the housing microenvironment. Haerbin City is a typical northen city of China with high mortality of lung cancer, among which adenocarcinoma

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accounts for about 50%. Our study showed that pulmonary adenocarcinoma is closely related to high CCI and the other four factors reflecting pollution of HME. This reflects indirectly the level of exposure and extent of pollution of HME. According to an estimation from a research institute in Shanghai(7), the amount of Bap exposure to the inhabitant who uses a coal stove as fuel in Shanghai is equal to the amount of Bap came from smoking 20 cigarettes per day. Our Conditional Logistic Regression Analysis showed that high CCI, WISP and low ceiling of a house are main risk factors for pulmanory adeno- carcinoma, and the ß value associated with these three factors increase significantly. This is easy to understand because a house with FVBK will cause the pollution of HME, low ceiling and high CCI will aggravate the pollution of HME. The results of indoor air determinations confirm that the pollution of HME is more serious in the families with high CCI. Gao, et al reported that the relative risk for women suffering from lung cancer living in a house full of smoke is 60% higher than that living in the house with no smoke or less smoke(8). Our results in this study are similar with that, and is consistent with the report in Xuanwei County (9). It must be mentioned that the OR value of WISP is as high as 15.19. This may be due to the high concentration of PAH contained in smog. According to a Japanese research report(10), there is a positive correlation between the onset of pulmonary adenocarcinoma and the concentration of PHA.

Owing to the small quantity of the cases, CPD and noxious occupational history reach significant level only when using single factor analysis. The relation between these factors and pulmonary adenocarcinoma is worthy of further research.

REFERENCES

1. Vincent RG. et al. The changing histopathology of lung cancer. Cancer 39:1647, 1977
2. Doll R., Peto R. Cigarette smoking and bronchial carcinoma: Dose and time relationship among regular and lifelong nonsmokers. J Epidemiol Community Hlth 32:303, 1978
3. Zheng, Wei, et al. Study of relation between cigarette smoking and pulmanory squamous carcinoma. Tumor 6:17, 1986
4. Hinds MW. et al. Difference in lung cancer risk from smoking among Japanese, Chinese and Hawaiian women in Hawaii. Int. J. Cancer 27:297, 1981
5. Yu, Songlin et al. Application of Conditional Logistic Regression Model in matched case-control study Chin J. Prev. Med. 19:292, 1985
6. Li, Zheng et al. Determination of quality and concentration of Bap in environmental air around living area-----paper chromatography fluorescent spectrophotometry. The Standard Bureau of China 1986
7. Huang, Yin et al. Pollution of indoor air by coal stove in different seasons and regularity of getting rid of pollution Shanghai Environmental Science 1:26, 1985

2023381734

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

8. Gao, Yutang, et al. Case-control study of 673 cases of female lung cancer in Shanghai urban district. Tumor 7:194, 1987
9. Preventive Medical Center of China: Air pollution determination in high morbidity area of lung cancer in Xuanwei County. Hygiene Research 13(2):20, 1984
10. Japanese Researcher: Relation between tissue typing of lung cancer and regional environmental characteristic. Compilation of Cancer Science Society of Japan 10: 495, 1985

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Lung cancer among women in north-east China

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Summary A case-control study of lung cancer involving interviews with 965 female patients and 959 controls in Shenyang and Harbin, two industrial cities which have among the highest rates of lung cancer in China, revealed that cigarette smoking is the main causal factor and accounted for about 35% of the tumours among women. Although the amount smoked was low (the cases averaged eight cigarettes per day), the percentage of smokers among women over age 50 in these cities was nearly double the national average. Air pollution from coal burning stoves was implicated, as risks of lung cancer increased in proportion to years of exposure to 'Kang' and other heating devices indigenous to the region. In addition, the number of meals cooked by deep frying and the frequency of smokiness during cooking were associated with risk of lung cancer. More cases than controls reported workplace exposures to coal dust and to smoke from burning fuel. Elevated risks were observed for smelter workers and decreased risks for textile workers. Prior chronic bronchitis/emphysema, pneumonia, and recent tuberculosis contributed significantly to lung cancer risk, as did a history of tuberculosis and lung cancer in family members. Higher intake of carotene-rich vegetables was not protective against lung cancer in this population. The findings were qualitatively similar across the major cell types of lung cancer, except that the associations with smoking and previous lung diseases were stronger for squamous/oat cell cancers than for adenocarcinoma of the lung.

The rate of lung cancer among Chinese females is among the highest in the world. Elevated incidence, particularly of adenocarcinoma of the lung, has been noted for Chinese females residing in different geographic areas, including Singapore (Law *et al.*, 1976), Hong Kong (Kung *et al.*, 1984), Shanghai (Gao *et al.*, 1988) and the United States (Hinds *et al.*, 1981). The high rates are unusual because few Chinese women smoke tobacco. Within China, elevated rates of female lung cancer are found in urban areas such as Shanghai and in rural as well as urban areas of the northeastern provinces of Liaoning and Heilongjiang (National Cancer Control Office, 1980; Xu *et al.*, 1986). Reasons for the geographic variation and clustering of high rates of lung cancer in the northern provinces are not known. We report here the results from case-control studies conducted in Shenyang and Harbin, the two major industrial cities in Liaoning and Heilonjiang provinces, to evaluate the role of several potential risk factors.

Methods

In 1985-87, investigators from the Liaoning Province Public Health and Anti-Epidemic Station and the US National Cancer Institute conducted a large lung cancer study including 1,517 males (729 cases, 788 controls) and 1,073 females (518 cases, 555 controls). During the same time period, investigators at Harbin Medical College and the University of Southern California conducted a case-control study focused on female lung cancer (446 cases, 404 controls). Investigators from both studies met during the planning phase of the study and adopted a unified protocol to ascertain and select cases and controls, and a common questionnaire for the interview component of the study. Data on risks from smoking and air pollution among men and women in Shenyang have been published elsewhere (Xu *et al.*, 1989). Herein we report risks among females associated with a variety of factors, increasing sample sizes by nearly 80% by combining information from the two cities.

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Case ascertainment

We sought to enrol all newly diagnosed primary lung cancers in females in the study areas between 1985 and 1987. Utilising the cancer registries of Harbin and Shenyang, a system of rapid case ascertainment was established with the cooperation of all the major hospitals serving its area (about 35 in each city). In brief, the admitting physicians at each participating hospital completed a case abstract form whenever a lung cancer was diagnosed. We received these abstracts on a bi-weekly basis and selected as eligible cases those with primary, incident lung cancers diagnosed among female residents of the study area who were aged less than 70 years at the time of diagnosis. The lung cancer diagnosis and cell-type classification were verified locally in each study area by a panel of pulmonary specialists and pathologists.

Control selection

Controls were females randomly selected from the general populations of Harbin and Shenyang. Controls were frequently matched by 5-year age group to the expected distribution of cases, which was determined in advance using the number and age distribution of female lung cancer cases reported in the two cities in 1983. A three-stage sampling procedure was used to select each control. The initial unit for randomisation was the neighbourhood committee, of which there are about 1,500 each in Harbin and in Shenyang. Committees were randomly selected with replacement after weighting by their population sizes. Then we randomly chose a household group from the approximately 10-25 household groups within each selected neighbourhood committee. In the final stage, among all females in the 5-year age category within the household group, one was randomly selected.

Questionnaire

A structured, pre-coded questionnaire was used by trained interviewers who conducted personal interviews with the participants in their homes or work sites or in the hospital/clinic. The interview gathered information on demographic factors, active and passive smoke exposure, lifetime residential and occupational histories, diet and cooking practices, personal history of nonmalignant lung disease, history of tuberculosis

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(TB) and cancer in first degree relatives, and reproductive factors. Questions on smoking included the amount and types of tobacco products smoked, age when smoking started, and for ex-smokers, age when smoking stopped. To assess passive smoke exposure, we asked about lifetime residential exposure to tobacco smoke from cohabitants, including the amount and duration of exposure from each smoking cohabitant. In addition, we asked if the subject was exposed to passive smoking at each work place. For each residence in which a subject lived for three or more years, we asked in detail about heating and cooking practices, including methods for heating and cooking and types of fuels used. Several questions were asked about 'Kang', brick beds commonly used in the north-eastern part of China, which are heated either directly by a stove underneath them or by pipes connected to the cooking stove. To assess dietary habits 5 years prior to interview, we asked subjects to estimate their frequencies of intake of 33 food items, including staple grains (rice, wheat, maize); soya bean products (bean curd, fermented bean paste), dried peas and beans, animal protein sources (eggs, fish, shellfish, liver, poultry, pork), fermented/salted foods, alcoholic beverages, and fresh vegetables and fruits. Also included were questions on diagnosis by a physician of previous each lung diseases, age at lung disease diagnosis, and if hospitalisation was required. Information on outcome of each pregnancy, age at menarche and at menopause was also elicited. As a quality-control measure, interviews were cassette-recorded for review by a field supervisor.

Statistical methods

The data were edited, coded, keypunched and submitted to computerised range and consistency checks. The statistical analyses were based on multivariate techniques for case-control data (Breslow & Day, 1980). Unconditional logistic regression analyses were used to estimate summary relative risks (RRs) of lung cancer associated with various factors while adjusting for other factors. RRs were calculated for all lung cancer combined and for specific cell types. We present results for squamous cell and oat/small cell cancers combined because we had too few oat/small cell cancers to conduct separate analysis and because these two cell types of lung cancer are more strongly associated with smoking than adenocarcinoma of the lung (Lubin & Blot, 1984). Our analysis for adenocarcinoma of the lung did not include large cell cancers. There were too few large cell cancers for inclusion by cell type. In the analyses including all subjects, the regression models contained terms for age (less than 50, 50–59, 60–69 years), education (no formal education, primary or secondary school, high school and higher), smoking (non-smoker, smoked 1–19 cigarettes per day and 1–29 years, 1–19 cigarettes per day and 30–39 years, 1–19 cigarettes per day and 40 + years, 20 + cigarettes per day and 1–29 years, 20 + cigarettes per day and 30–39 years, 20 + cigarettes per day and 40 + years) and study centre (Harbin versus Shenyang). We also conducted analyses restricted to nonsmokers, deleting the smoking variables in the regression model and adjusting only on age, education, and centre.

Results

All interviews were conducted in 1985–87. At the close of case recruitment, 1,049 eligible patients had been identified by the Harbin and Shenyang cancer registries. Nine-hundred and sixty-four (91.8%) were interviewed, 32 (3.1%) died before our attempted contact, 50 (4.8%) were not located and three (0.3%) refused to participate.

Forty-two per cent ($n = 405$) of the cases were diagnosed by tissue biopsy, 32% ($n = 309$) by cytology, and 26% ($n = 351$) by radiology. Although the percentages of pathologically and cytologically confirmed cases were higher in Shenyang than in Harbin, the cell-type distributions were similar. In the combined set of cases, there were 44% ($n = 310$) adenocarcinomas, 28% ($n = 201$) squamous cell carcinomas, 16% ($n = 117$) oat/small cell carcinomas and the remainder were large cell carcinomas, mixtures of other cell types or the cell type was not known ($n = 66$).

A total of 959 controls (404 in Harbin, 555 in Shenyang) were interviewed. Cases (mean age 55.9 years) and controls (mean age 55.4 years) were closely matched on age but cases were less educated than controls. Relative to those with no formal education, the RRs for women with primary/junior school, high school technical school or college education was 0.9, 1.0, 0.8 respectively (RR for linear trend 0.9; 95% CI 0.8–1.0).

Smoking habits

Table I shows the percentages of women by 5-year age group who smoked cigarettes for 6 months or longer. The prevalence of smoking in the general population (i.e. among controls) varied with age, being much higher (approximately 40%) among women 50 or over than among women below 50 (smoking rate 24%), but increased risks were seen in smokers at all ages. For all lung cancers combined, smokers experienced a 2.3-fold (95% CI 1.9–2.8) increased risk of lung cancer. The age-, education- and city-adjusted RRs for smoking were 4.2 (95% CI 3.0–5.9) for squamous cell cancer, 2.2 (95% CI 1.4–3.2) for oat/small cell cancers, 1.5 (95% CI 1.1–1.9) for adenocarcinoma of the lung and 2.5 (95% CI 1.9–3.3) for the 'other' category which included those diagnosed clinically, large cell cancers, and those with mixed or unknown cell type. Most (57%) cases began smoking before they were 20 years old, compared to 40% of controls; the average age when subjects began to smoke was 19.9 for cases and 24.0 for controls. The women were not heavy smokers. Few subjects (9% cases, 4% controls) smoked 20 or more cigarettes per day, and the mean daily number of cigarettes smoked was 8.1 for cases and 6.8 for controls. Nevertheless, there was sufficient variation in amounts smoked to show that risks of lung cancer significantly ($P < 0.001$) increased with increasing numbers of cigarettes smoked per day and with increasing duration of smoking (Table II). Clear independent effects were seen with each measure of smoking exposure within categories of the other, with the associations stronger for squamous/oat cell carcinomas than for adenocarcinoma. At the same level of smoking, 2- to 4-fold differences in the magnitude of the risk between the two cell types were typically observed.

Passive smoking

Table III shows the RRs associated with passive smoke exposure, first among all subjects after adjusting for personal smoking and then among non-smokers. Eighty-eight per cent of all cases and controls reported having lived in at least one of their residences with a cohabitant who was a smoker. There were no significant case-control differences in ever having lived with a smoker, except for non-smokers who lived with a spouse who smoked, where the risk was reduced (RR 0.7; 95% CI 0.6–0.9). The lowered risk associated with a spouse who smoked was seen only in Harbin: 60% of non-smoking controls and 46% of non-smoking cases in Harbin reported that the spouse ever smoked, compared to 52% of non-smoking controls and 52% of non-smoking

Table I Prevalence of smoking by 5-year age groups and corresponding relative risks for lung cancer associated with smoking

	Cases		Controls			
Age (years)	n	% smokers	n	% smokers	RR	(95% CI)
< 50	208	34	163	24	1.6	(1.0, 2.6)
50–54	203	60	196	35	2.7	(1.8, 4.0)
55–59	232	62	241	43	2.0	(1.4, 3.0)
60–64	184	68	191	39	3.2	(2.1, 5.0)
65 +	137	60	161	40	2.2	(1.4, 3.5)

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Table II RR and 95% CI for lung cancer associated with intensity of smoking by cell type

Cell type	Cigarettes per day	Duration of smoking (years) 1–29		30–39		≥40	
All lung cancer	1–19	1.3 (1.0, 1.7)[a]	(118/125)[b]	2.6 (1.9, 3.5)	(146/83)	3.2 (2.4, 4.3)	(187/103)
	≥20	1.8 (0.9, 3.6)	(19/14)	3.3 (1.8, 6.2)	(33/15)	5.7 (2.9, 11.5)	(36/11)
Squamous/oat cell	1–19	2.0 (1.3, 2.9)	(48/125)	3.9 (2.6, 5.9)	(56/83)	4.7 (3.1, 7.1)	(64/103)
	≥20	2.0 (0.7, 5.4)	(6/14)	3.8 (1.7, 8.8)	(10/15)	12.0 (5.3, 27.0)	(17/11)
Adenocarcinoma	1–19	0.8 (0.5, 1.3)	(30/125)	1.7 (1.1, 2.5)	(37/83)	2.0 (1.3, 3.0)	(45/103)
	≥20	0.8 (0.3, 2.6)	(4/14)	3.8 (1.8, 8.0)	(15/15)	2.8 (1.0, 7.4)	(7/11)

[a]95% confidence intervals. [b]Numbers of cases/controls are in parentheses.

Table III RR for lung cancer associated with passive smoke exposure

Source of passive smoke exposure	Passive smoke exposure	All subjects Case/controls	RR[a]	Non-smokers only Case/controls	RR[a]
Any cohabitant	no	112/111		74/87	
	yes	844/842	0.8	343/515	0.7
Spouse	no	398/402		212/271	
	yes	558/551	0.9	205/331	0.7[b]
Mother	no	543/595		298/410	
	yes	413/358	1.0	119/192	0.9
Father	no	484/515		235/352	
	yes	472/438	1.0	182/250	1.1
Workplace	no	403/448		187/301	
	yes	563/513	1.2	228/301	1.1

[a]Adjusted for age, education, personal smoking and study area. [b]Adjusted for age, education, and study area. [c]$P < 0.05$.

cases in Shenyang. There were no significant trends in risk with intensity (i.e. number of cigarettes smoked by family members) and duration of exposure (i.e. years of smoking by cohabitants), except for an increasing risk associated with increasing intensity of father's smoking in the presence of the index subject.

There was a small excess risk associated with passive smoke exposure at the workplace. For all subjects, the smoking-adjusted RR was 1.2 (95% CI 1.0–1.4). The result was similar for non-smokers (RR 1.1; 95% CI 0.9–1.6). There were no significant dose–response trends associated with years of passive smoke exposure at work.

Heating and cooking practices

Table IV presents RRs associated with duration of use of Kang and other heating devices. Elevated risks were observed for increasing years of use of Kang (particularly when heated by stoves underneath), heated brick walls or floors (i.e. heated by pipes leading from the stoves to the wall or floor), coal stoves and coal burners. On the other hand, decreased risks were observed for increasing years of use of non-coal-burning stoves and central heating. The patterns were generally similar for smokers and non-smokers, and for squamous/oat cell carcinomas and adenocarcinoma. We also examined the risks associated with years when coal, wood, and central heating served as the main fuel for heating. The RRs tended to rise with increasing use of coal and decline with increasing use of wood and central heating, but none of the trends was significant.

Cases more often reported that their homes became smoky during cooking and that they more frequently had irritated eyes during cooking (Table V). There also was a significant trend in risk with increasing number of meals cooked by deep frying, although this method of cooking was not frequently used. The results were similar for squamous/oat cell cancers and adenocarcinoma, and for smokers and non-smokers.

Occupation

Subjects were asked about all jobs in which they had worked 1 or more years, with cases and controls compared in terms of their employment in 29 job categories. Most (77%) women held at least one job outside the home, but significantly increased risks were observed only for metal smelting work (RR 1.5; 95% CI 1.0–2.1), while a significantly decreased risk was observed for textile workers (RR 0.6; 95% CI 0.3–1.0). The women were also asked if they were exposed to 12 specific dusts, smoke or fumes at work, with from 1 to 16% reporting on-the-job exposures to the 12 pollution items. Cases reported exposure to coal dust (RR 1.5; 95% CI 1.1–2.0) and to smoke from burning fuel (RR 1.6; 95% CI 1.2–2.2) significantly more often.

Table IV Relative risk of lung cancer associated with years of use of specific heating devices

Exposure (years)	Case/controls	RR[a] (95% CI)
Kang		
0	25/40	1.0
1–39	384/376	1.4 (0.8, 2.4)
40–49	132/144	1.1 (0.6, 2.8)
50+	415/393	1.6 (0.9, 2.8)
Burning Kangs		
0	677/740	1.0
1–20	106/91	1.2 (0.9, 1.7)
21+	173/122	1.5 (1.1, 2.0)
Coal stoves		
0–20	192/226	1.0
21–40	511/485	1.2 (1.0, 1.6)
41+	253/242	1.3 (1.0, 1.7)
Non-coal stoves		
0	212/183	1.0
1–20	367/340	0.8 (0.6, 1.1)
21–30	259/295	0.7 (0.5, 0.9)
31+	118/135	0.8 (0.5, 1.1)
Heated brick walls/floors		
0	586/651	1.0
1–20	127/98	1.5 (1.1, 2.1)
21+	243/204	1.4 (1.1, 1.9)
Coal burners		
0	525/583	1.0
1–20	258/202	1.2 (1.0, 1.6)
21+	173/168	1.1 (0.8, 1.4)
Central heat		
0	602/573	1.0
1–20	215/200	1.0 (0.8, 1.3)
21+	139/180	0.8 (0.6, 1.0)

[a]Adjusted for age, education, personal smoking and study area.

Table V Relative risk of lung cancer associated with frequency of deep frying and eye irritation when cooking

	Cases/controls	RR[a] (95% CI)
Deep fry (times per month)		
0	324/403	1.0
1	326/360	1.2 (1.0, 1.5)
2	170/107	2.1 (1.5, 2.8)
3+	121/81	1.9 (1.4, 2.7)
Eye irritation		
never/rarely	647/732	1.0
sometimes	218/163	1.6 (1.2, 1.8)
frequent	89/56	1.8 (1.3, 2.6)

[a]Adjusted for age, education, personal smoking and study area.

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Prior lung disease

Table VI lists RRs of lung cancer associated with specific prior chronic lung diseases. Lung diseases that were first diagnosed within three years of lung cancer diagnosis (and a comparable time period for controls) were excluded from the analysis. After adjusting for smoking, history of any prior lung disease was associated with a 50% increased risk (95% CI 1.2–1.8). The excess was greatest for pneumonia (RR 2.1). An increased risk was found for bronchitis and/or emphysema, but the association was limited to squamous/oat cell cancers (RR 1.6) and not found for adenocarcinoma (RR 0.9).

We investigated whether risk of lung cancer varied according to the lag time following the diagnosis of prior lung disease. Earlier detection of chronic bronchitis/emphysema conveyed greater risk. Relative to those with no history of chronic bronchitis/emphysema, the RRs were 1.3, 1.3, and 1.7 respectively for conditions detected 4–10, 11–20, and 21 + years before lung cancer diagnosis. On the other hand, the RRs were higher for more recent diagnoses of pneumonia and TB. The RRs were 2.7, 2.5 and 1.8 respectively for pneumonia, and 2.8, 1.1, and 1.2 for TB first detected 4–10, 11–20 and 21 + years prior to lung cancer diagnosis. The elevated risk associated with TB diagnosed 4–10 years prior to lung cancer was significant; it was observed for both squamous/oat cell cancers and adenocarcinoma of the lung, and among non-smokers as well as smokers.

Family history of TB and cancer

We observed a significant 60% (95% CI 1.2–2.1) increased risk associated with TB in a household member, with similar risks for squamous/oat cell cancers and adenocarcinoma. The familial association was seen in smokers and non-smokers, and remained unchanged after adjusting for personal history of TB. The risk associated with family history of TB increased with decreasing age when the index subject was first exposed. After adjusting for smoking, exposures at age <21, 21–30 and >30 conferred risks of 1.7, 1.5 and 1.2 when compared to those with no household TB exposure.

Family history of lung cancer in first degree relatives, reported by 4.5% of the cases, was associated with a significant 80% (95% CI 1.1–3.0) increased risk. There was little difference in risk by cell type or smoking status. The risk of lung cancer was somewhat higher among those with a family history of other cancers (RR 1.4; 95% CI 1.0–2.0), with the excess risk being higher for adenocarcinoma (RR 1.8) than for squamous/oat cell cancers (RR 1.1).

Menstrual and reproductive factors

Table VII presents risks of lung cancer by various menstrual and reproductive factors. There were little or no association with age at menarche, parity, hysterectomy, spontaneous abortion, pregnancy resulting in difficult labour, and use of oral contraceptives. There was a significant 50% (95% CI 1.2–1.8) increased risk associated with history of miscarriage, and cases tended to have a later age at natural menopause although the trend was not smooth.

Table VII Relative risks of lung cancer associated with menstrual and reproductive factors

	Cases/controls	RR* (95% CI)
Age at menarche		
18 +	184/192	1.0
16–17	427/412	1.1 (0.8, 1.4)
14–15	285/276	1.1 (0.8, 1.4)
<14	55/64	0.9 (0.6, 1.4)
Number of children		
<3	193/205	1.0
3–4	319/300	1.1 (0.9, 1.5)
5–6	275/272	1.0 (0.8, 1.4)
7 +	169/174	1.0 (0.7, 1.3)
Age at natural menopause		
<45	77/112	1.0
45–49	373/303	1.7 (1.2, 2.4)
50–54	278/327	1.3 (0.9, 1.8)
55 +	31/28	1.7 (1.0, 3.2)
Positive history of		
Hysterectomy	36/36	1.0 (0.6, 1.6)
Miscarriage	82/126	1.5 (1.2, 1.8)
Spont. abortion	239/218	1.1 (0.9, 1.4)
Difficult labour	76/61	1.3 (0.9, 1.8)
Oral contraceptive	54/68	0.8 (0.5, 1.2)

*Adjusted for age, education, personal smoking and study area.

Dietary factors

The diet of the subjects was dominated by staple grains (median intake among controls = 1,095 times per year), fresh vegetables (1,188 times per year), fermented salted foods (730 times per year), and soya bean products (365 times per year). Less frequent was consumption of animal protein sources (231 times per year), fresh fruits (52 times per year), and peas and beans (12 times per year). Risks of lung cancer in relation to dietary intake are shown in Table VIII. Higher frequencies of intake of vegetables, either those rich or low in carotene content were not significantly protective against lung cancer. The three foods with the highest carotene content in this study population were dried hot red peppers (16.9 mg of carotene per 100 g), dark leafy greens (2.7 mg of carotene per 100 g), and carrots (2.0 mg of carotene per 100 g). Carrots and dried hot red peppers were consumed less often by cases compared to controls, but these items were not frequently consumed (mean intake among controls was 41.4 and 70.0 times per year respectively). On the other hand, cases had slightly higher intakes of the more commonly consumed dark leafy greens (average intake among controls was 163.5 times per year).

Cases reported higher frequencies of intake of animal protein and fresh fruits. Few women (12% cases versus 8% controls) drank alcohol more than once a year, but they showed a significant smoking-adjusted 30% increased risk of lung cancer compared to those who did not drink at all. However, there was no clear trend with increasing alcohol consumption. There were no appreciable differences in dietary patterns for squamous/oat cell cancers versus adenocarcinoma, nor for smokers versus non-smokers.

Table VI Relative risk for lung cancer associated with previous lung diseases

	All lung		Squamous/oat		Adenocarcinoma	
	Cases/controls	RR* (95% CI)	N°	RR*	N°	RR*
Positive history of:						
chronic bronchitis and/or emphysema	210/137	1.4 (1.2, 1.8)	79	1.6†	46	0.9
pneumonia	66/28	2.1 (1.3, 3.3)	23	2.3†	15	1.6
tuberculosis	103/83	1.3 (0.9, 1.7)	33	1.2	33	1.1

*Adjusted for age, education, personal smoking and study area. °Number of cases with factor. †95% confidence intervals excludes 1.0.

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Table VIII Relative risk of lung cancer associated with dietary factors

Dietary factor	Intake (times per year)	Case/control	RR[a] (95% CI)
Staple grain	< 1095	308/266	1.0
	1095 - 1146	352/396	0.8 (0.7, 1.1)
	> 1146	290/290	0.9 (0.7, 1.2)
Peas and beans	< 4	256/241	1.0
	4 - 15	221/244	0.9 (0.7, 1.2)
	16 - 52	319/314	1.1 (0.8, 1.4)
	> 52	160/152	1.0 (0.7, 1.3)
Soya bean products	< 153	232/217	1.0
	153 - 365	204/266	0.7 (0.5, 0.9)
	366 - 485	265/250	0.9 (0.7, 1.2)
	> 485	255/219	1.0 (0.8, 1.3)
Animal protein	< 109	156/238	1.0
	109 - 230	229/236	1.6 (1.2, 2.1)
	231 - 442	235/237	1.6 (1.2, 2.1)
	> 442	336/241	2.3 (1.7, 3.0)
Fermented/salted foods	< 366	234/273	1.0
	366 - 625	179/154	1.2 (0.9, 1.6)
	626 - 990	329/306	1.2 (0.9, 1.5)
	> 990	214/219	0.9 (0.7, 1.2)
Vegetables[b] low in carotene content	< 366	254/251	1.0
	366 - 547	256/251	1.0 (0.8, 1.3)
	548 - 730	248/240	1.0 (0.8, 1.3)
	≥ 731	198/210	0.8 (0.6, 1.1)
Vegetables[c] high in carotene content	< 731	201/223	1.0
	731 - 1095	355/331	1.1 (0.9, 1.4)
	1096 - 1460	195/197	1.0 (0.8, 1.3)
	≥ 1461	205/201	0.9 (0.7, 1.2)
Fresh fruits	< 19	203/232	1.0
	19 - 52	209/249	1.0 (0.8, 1.3)
	53 - 132	256/231	1.4 (1.0, 1.8)
	> 132	288/240	1.5 (1.2, 2.0)
Alcohol beverages	0	649/706	1.0
	1 - 12	110/96	1.3 (0.9, 1.7)
	13 - 52	81/76	1.0 (0.7, 1.5)
	> 52	116/75	1.3 (1.0, 1.8)

[a]Adjusted for age, education, personal smoking and study area. [b]Includes white potato, pale sweet potato, white vegetables, yellow and green gourds. [c]Includes salted vegetables, dark sweet potato, yellow green squash, dark green leafy greens, yellow and light green leafy vegetables, carrots, red peppers, dried hot red peppers, green peas, tomatoes.

Multivariate analysis

The factors found to have a significant effect on risk of lung cancers in univariate analysis were evaluated simultaneously in multivariate unconditional logistic regression analysis. In addition to smoking, the following variables had a significant effect on risk of lung cancer ($P < 0.05$) and they entered the regression model in the order as shown: deep-frying, eye irritation, pneumonia, household tuberculosis, burning Kang, self-reported occupational exposure to burning fuel, passive smoking from any household member and heated brick wall/floor.

Discussion

This population-based case–control study conducted in two large northern Chinese cities revealed that at least 35% of the lung cancers among women can be explained by cigarette smoking. Although this attributable risk is low compared to Caucasian female populations (Lubin & Blot, 1984), it is higher than elsewhere in China (Chan *et al.*, 1979; Gao *et al.*, 1988), mainly because of a higher prevalence of smoking women in this region. Smoking rates among women over age 50 were nearly double those found in Shanghai or nationally in China (Gao *et al.*, 1988; Weng *et al.*, 1987). Furthermore, women in Harbin and Shenyang started to smoke at a relatively young age. As compared to women in Shanghai, where 19% of female smokers in the general population began smoking at age 19 or younger, approximately 40% started at this age in northern China. Hence, even though amounts smoked were low (averaging eight cigarettes per day among the cases), smoking contributes to the elevated rates of lung cancer among northern Chinese women. It also appears to account for the higher percentage (44%) of squamous/oat cell cancers in our study versus 32% and 35%, respectively, in Shanghai and Hong Kong (Gao *et al.*, 1988; Kung *et al.*, 1984). The relatively low mean daily number of cigarettes smoked by these women may explain the lower relative risks of lung cancer among Chinese compared to Caucasian smokers.

We observed no overall association between lung cancer risk and passive smoking. Our results varied by source of passive smoke exposure, however, with non-smoking cases reporting less exposure from spouses (but only in Harbin), more exposure from fathers, and similar exposure from mothers when compared to non-smoking controls. Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognised as a cause of lung cancer around the world (Surgeon General, 1986). Perhaps in this study population the effects of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighbourhood air pollution (Xu *et al.*, 1989).

Pollution from coal burning seems likely to contribute to north-eastern China's elevated lung cancer rates. Risks increased with increasing years of use of burning Kang and heated brick walls/floors, and we observed weaker but similar trends with use of coal stoves and coal burners. Levels of air pollution have been reported to be high in both Harbin and Shenyang, with both indoor and outdoor wintertime benzopyrene concentrations exceeding standards for cities in the United States by more than 60-fold (Dai *et al.* personal communication; Xu *et al.*, 1989). Coal burning, especially use of a local smoky coal, has also been implicated in the high lung cancer rates reported among women in Xuan Wei County in southern China (Mumford *et al.*, 1987).

The effects of certain workplace exposures on lung cancer resemble those reported in Shanghai (Levin *et al.*, 1987, 1988), including a decreased risk seen in textile workers. The excess risk among women employed in metal smelting is consistent with the three-fold increased risk among men exposed to inorganic arsenic in copper smelting in Shenyang (Xu *et al.*, 1989) and the United States (Lubin *et al.*, 1981). The occupational findings will be presented in more detail in a separate report.

Our findings that cases were more likely to cook food by deep frying and to more frequently report eye irritation when they cooked are consistent with the increased risks associated with exposure to cooking oil fumes in Shanghai (Gao *et al.*, 1987). The association in Shanghai was strongest for use of rapeseed cooking oil, but few women in Harbin or Shenyang used this type of oil, suggesting that vapors from several types of cooking oils may be linked to increased risk. Condensates of both rapeseed and soya bean cooking oil volatiles have been found to be mutagenic (Qu *et al.*, 1986). Further short-term testing of several types of cooking oils is underway to help identify the responsible constituents and provide leads for additional study.

Certain lung diseases may have an aetiologic role in lung cancer development (Gao *et al.*, 1987; Wu *et al.*, 1988). Such an association is of particular importance in China, where the prevalence of chronic lung disease is high. Indeed we found that 35% of the cases and 24% of the controls reported prior chronic lung disease. Like others, we found an excess risk of squamous/oat cell cancers of the lung, but not adenocarcinoma, in association with chronic bronchitis/emphysema. Our finding of a significant increased risk associated with recent diagnosis of TB (i.e. 4–10 years prior to lung cancer) is consistent with results from Shanghai (Zheng *et al.*, 1988).

Our results are supportive of a familial tendency in lung cancers (Cohen *et al.*, 1977; Ooi *et al.*, 1986*a,b*; Skillrud *et al.*, 1987; Wu *et al.*, 1988). Shared environmental exposures, familial aggregation of smoking habits, and/or genetic predisposition may be important. The percentage of cases having

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affected first-degree family members was small (4%). Recent case-control studies in Great Britain (Ayesh *et al.*, 1984) and the United States (Caporaso *et al.*, 1989), however, suggest that genetic traits may influence susceptibility in a sizeable portion of cases. These investigations revealed significantly increased risks of lung cancer associated with the genetically controlled ability to extensively metabolise the drug debrisoquine, a trait affecting 54% of the control population studied in the United States.

We found no strong support for a role of hormonal factors for lung cancer overall or specifically for adenocarcinoma. The cases did tend to experience menopause at later ages, but the trend in risk with age at menopause was not smooth. History of prolonged labour or hysterectomy, which had been suspected as risk factors for adenocarcinoma because of the potential for trauma-associated lung embolism, occurred more frequently among our cases, but the excess risks were not significant since relatively few women were affected. Risk of lung cancer was recently reported to be increased among Chinese women with short menstrual cycle length (Gao *et al.*, 1988), but this variable was not assessed in the current study.

In other countries the risk of lung cancer is generally reduced among those with higher dietary intake of carotenoids (Ziegler, 1989), but our findings are less clear. Cases had slightly higher rather than lower intake of dark green leafy vegetables, the most commonly consumed rich source of carotene. Moreover, in our analysis using a combined index of all vegetables rich in carotene, high frequencies of intake did not confer a significant protective effect. Reasons for the absence of protective effects are not clear. A possible explanation is that three-fourths of the study population ate vegetables high in carotene content at least twice a day so that the nearly uniformly high intake of carotene-containing foods limited variability and hindered detection of an effect. Data on plasma carotene levels from this study population will be important as a more objective measure of their dietary intake. Misclassification of intake also may have dampened trends. We did not have information on portion size and the highest carotene-containing food in this population is dried hot red peppers, usually used as a condiment. In addition, recall of past diet may have been influenced by recent dietary improvements, perhaps more so among cases who may have been given preferential dietary treatment because of their illness.

In summary, this investigation revealed that contrary to *a priori* expectation in China, cigarette smoking is the major cause of lung cancer among women in north-east China and contributes to the area's high rates of mortality from this tumor. Prevention activities should emphasise smoking cessation, while additional study may help clarify the role of indoor and outdoor air pollution, chronic non-malignant lung disease, occupational exposures, familial susceptibility and other factors in the aetiology of lung cancer.

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References

AYESH, R., IDLE, J., RITCHIE, J.C., CROTHERS, M.J. & HETZEL, M.R. (1984). Metabolic oxidation phenotypes as markers for susceptibility to lung cancer. *Nature*, 312, 169.

BRESLOW, N.E. & DAY, N.E. (1980). *Statistical Methods in Cancer Research: the Analysis of Case-Control Studies*. IARC: Lyon.

CAPORASO, N.E., FALK, R.T., ISSAQ, H.J. & 5 others (1989). Lung cancer risk, occupational exposure, debrisoquine metabolic phenotype. *Cancer Res.*, 49, 3675.

CHAN, W.C., COLBURNE, M.J., FUNG, S.C. & HO, H.C. (1979). Bronchial cancer in Hong Kong 1976-1977. *Br. J. Cancer*, 39, 182.

COHEN, B.J., DIAMOND, E.L., GRAVES, C.G. & 6 others (1977). A common familial component in lung cancer and chronic obstructive pulmonary disease. *Lancet*, ii, 523.

ERSHOW, A.G. & CHEN, W.K. (1990). Chinese food composition tables: a translation with English common names, Latin scientific names, and Pinyin romanized transliterations. *Food Comp. Anal.* (in the press).

GAO, Y.T., BLOT, W.J., ZHENG, W. & 5 others (1987). Lung cancer among Chinese women. *Int. J. Cancer*, 40, 604.

GAO, Y.T., BLOT, W.J., ZHENG, W., FRAUMENI, J.F. & HSU, C.W. (1988). Lung cancer and smoking in Shanghai. *Int. J. Epidemiol.*, 17, 277.

HINDS, M.W., STEMMERMANN, G.N., YANG, H.Y. & 3 others (1981). Differences in lung cancer from smoking among Japanese, Chinese and Hawaiian women in Hawaii. *Int. J. Cancer*, 27, 297.

KUNG, I., SO, K. & LAM, T. (1984). Lung cancer in Hong Kong Chinese: mortality and histologic types 1973-1982. *Br. J. Cancer*, 50, 381.

LAW, C.H., DAY, N.E. & SHANMUGARATNAM, K. (1976). Incidence rates of specific histological types of lung cancer in Singapore Chinese dialect groups, and their aetiological significance. *Int. J. Cancer*, 17, 304.

LUBIN, J.H. & BLOT, W.J. (1984). Assessment of lung cancer risk factors by histologic category. *J. Natl Cancer Inst.*, 73, 383.

MUMFORD, J.L., HE, X.Z., CHAPMAN, R.S. & 9 others (1987). Lung cancer and indoor air pollution in Xuan Wei, China. *Science*, 235, 217.

NATIONAL CANCER CONTROL OFFICE (1980). *Nanjing Institute of Geography Atlas of Cancer Mortality in the People's Republic of China*. China Map Press: Beijing.

OOI, W.L., ELSTON, R.C., CHEN, V.W., BAILEY-WILSON, J.E. & ROTHSCHILD, H. (1986). Increased familial risk for lung cancer. *J. Natl Cancer Inst.*, 76, 217.

OOI, W.L., ELSTON, R.C., CHEN, V.W., BAILEY-WILSON, J.E. & ROTHSCHILD, H. (1986). Familial lung cancer-correcting an error in calculation. *J. Natl Cancer Inst.*, 77, 990.

QU, Y.H., XU, G.X., HUANG, F., FANG, J.C. & GAO, Y.T. (1986). An Ames test on other by-products of the heating of cooking oils. *Tumor*, 6, 58.

SKILLRUD, D.M., OFFORD, K.P. & MILLER, R.D. (1986). Higher risk of lung cancer in chronic obstructive pulmonary disease: a prospective matched controlled study. *Ann. Intern. Med.*, 105, 503.

SURGEON GENERAL (1986). *The Health Consequences of Involuntary Smoking*. Department of Health and Human Services (CDC). Publication Number 87-3898. Government Printing Office: Washington, D.C.

WENG, X.Z., HONG, Z.G. & CHEN, D.Y. (1987). Smoking prevalence in Chinese aged 15 and above. *Chin. Med. J.*, 100, 186.

WU, A.H., YU, M.C., THOMAS, D.C., PIKE, M.C. & HENDERSON, B.E. (1988). Personal and family history of lung disease as risk factors for adenocarcinoma of the lung. *Cancer Res.*, 48, 7279.

XIAO, H. & XU, Z.Y. (1985). Air pollution and lung cancer in Liaoning Province, People's Republic of China. *NCI Monogr.*, 69, 53.

XU, Z.Y., BLOT, W.J., XIAO, H.P. & 7 others (1989). Smoking, air pollution and the high rates of lung cancer in Shenyang, China. *J. Natl Cancer Inst.*, 81, 1800.

ZHENG, W., BLOT, W.J., LIAO, M.L. & 5 others (1987). Lung cancer and prior tuberculous infection in Shanghai. *Br. J. Cancer*, 56, 501.

ZIEGLER, R.G. (1989). A review of epidemiologic evidence that carotenoids reduce the risk of cancer. *J. Nutr.*, 199, 116.

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(6) WEWER UM, TARABOLETTI G, SOBEL ME, ET AL: Role of laminin receptor in tumor cell migration. Cancer Res 47:5691-5698, 1987
(7) RAHMAN A, FUMAGALLI A, GOODMAN A, ET AL: Potential of liposomes to ameliorate anthracycline-induced cardiotoxicity. Semin Oncol 11:45-55, 1984
(8) PANNEERSELVAM M, WELT S, OLD LJ, ET AL: A molecular mechanism of complement resistance of human melanoma cells. J Immunol 136:2534-2541, 1986
(9) PINTO AL, LIPPARD SJ: Binding of the antitumor drug *cis*-diamminedichloroplatinum(II) (cisplatin) to DNA. Biochim Biophys Acta 780:167-180, 1985
(10) LESERMAN LD, BARBET J, KOURILSKY F, ET AL: Targeting to cells of fluorescent liposomes covalently coupled with monoclonal antibody or protein A. Nature 288:602-604, 1980
(11) LESERMAN LD, MACHY P, BARBET J: Cell specific drug transfer from liposomes bearing monoclonal antibodies. Nature 293:226-228, 1981
(12) HUANG A, KENNEL SJ, HUANG L: Interaction of immunoliposomes with target cells. J Biol Chem 258:14034-14040, 1983
(13) BRAGMAN KS, HEATH TD, PAPAHADJOPOULOS D: Simultaneous interaction of monoclonal antibody-targeted liposomes with two receptors on K562 cells. Biochim Biophys Acta 730:187-195, 1983
(14) TERRANOVA VP, RAO CN, KALEBIC T, ET AL: Laminin receptor on human breast carcinoma cells. Proc Natl Acad Sci USA 80:444-448, 1983
(15) LIOTTA LA, HAND PM, RAO CN, ET AL: Monoclonal antibodies to the human laminin receptor recognize structurally distinct sites. Exp Cell Res 156:117-126, 1985
(16) MIDDLEMAN E, LUCE J, FREI E III: Clinical trials with Adriamycin. Cancer 28:844-850, 1971
(17) RAHMAN A, ROH JK, TREAT J, ET AL: Clinical pharmacology of liposome encapsulated doxorubicin (LED) in phase I trials. Proc ASCO 6:31, 1987
(18) TREAT J, FORST D, WOOLLEY PV, ET AL: Liposome encapsulated doxorubicin (LED): A phase II study in measurable recurrent breast cancer patients. Proc ASCO 7:41, 1988
(19) LOPEZ-BERESTEIN G, FAINSTEIN V, HOPFER R, ET AL: Liposomal amphotericin B for the treatment of systemic fungal infections in patients with cancer: A preliminary study. J Infect Dis 151:704-710, 1985

Smoking, Air Pollution, and the High Rates of Lung Cancer in Shenyang, China

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A case-control study involving interviews with 1,249 patients with lung cancer and 1,345 population-based controls was conducted in Shenyang, an industrial city in northeastern China, where mortality rates are high among men and women. Cigarette smoking was found to be the principal cause of lung cancer in this population, accounting for 55% of the lung cancers in males and 37% in females. The attributable risk percentage among females is high compared to elsewhere in China, largely because of a higher prevalence of smoking among women. After adjustment for smoking, there were also significant increases in lung cancer risk associated with several measures of exposure to air pollutants. Risks were twice as high among those who reported smoky outdoor environments, and increased in proportion to years of sleeping on beds heated by coal-burning stoves (kang), and to an overall index of indoor air pollution. Threefold increases in lung cancer risk were found among men who worked in the nonferrous smelting industry, where heavy exposures to inorganic arsenic have been reported. The associations with both smoking and indoor air pollution were stronger for squamous cell and small cell carcinomas than for adenocarcinoma of the lung. Risks due to smoking or air pollution were not greatly altered by adjustment for consumption of fresh vegetables or sources of beta carotene or retinol, prior chronic lung diseases, or education level. The findings suggest that smoking and environmental pollution combine to account for the elevated rates of lung cancer mortality in Shenyang. [J Natl Cancer Inst 81:1800-1806, 1989]

A distinctive geographic gradient for lung cancer mortality exists in China, particularly among females (*1,2*). Mortality rates are elevated in northern provinces, with the highest rates occurring in both sexes in Liaoning. The exceptionally high rates among Liaoning women result in a male-to-female ratio in lung cancer mortality of 1:6, one of the lowest in the world (*3*). A correlation study linking lung cancer death rates and measures of industrial activity in 10 cities of Liaoning suggested that, even after smoking was taken into account, atmospheric pollution may contribute to lung cancer risk (*4*). To evaluate determinants of the elevated mortality and to test hypotheses regarding pollutant exposure as a risk factor for

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lung cancer, we conducted a case-control study in Shenyang, the industrial capital of Liaoning.

Methods

Subjects

During the period from September 1985 to September 1987, all newly diagnosed cases of primary lung cancer (9th revision, ICD 162) among residents of urban Shenyang aged 30-69 years were sought for enrollment in the study. Patients were identified by a rapid cancer reporting and referral system established for this study. The system involved all of the area hospitals, each of which reported to the Shenyang Cancer Registry. All diagnoses and histologic or cytologic slides of cases were reviewed by a special study group that met weekly through the study period. The group included pulmonary disease physicians (five) and senior pathologists (four).

Population-based controls, frequency-matched to the expected (based on earlier cancer registry data) age and sex distribution of the cases, were selected from the Shenyang urban area by a three-stage stratified random sampling scheme. The initial unit for randomization was the neighborhood committee—a geographic area defined by the municipal government. To select a control in a particular sex and 5-year age category, a neighborhood committee was sampled with replacement, weighting by its population, from among the 1,404 in Shenyang. Then, a household group within the committee was randomly chosen. Each committee typically encompasses 10-25 household groups and represents about 100 persons. In the final stage, among all persons in the specific sex and age category within the household group, one person was randomly selected.

Data Collection and Coding

Personal interviews with the subjects were conducted in the subject's home, the hospital-clinic, or the work site. The interviewers were experienced nurses aged 45-55 years who were employed and trained for this study. All interviews were recorded on cassettes for later review by a field supervisor. A structured, precoded questionnaire inquired about demographic characteristics, residential and occupational histories, smoking, diet (inquiring about the frequency of consumption, approximately 5 yr prior to interview, of 33 commonly eaten food items) and cooking practices, prior pulmonary conditions, and family history of cancer. Smokers were defined as those who had ever smoked cigarettes (commercial or handrolled) for 6 months or longer. Detailed information was obtained on potential exposure to indoor and outdoor air pollution, including information on housing and environmental conditions of every residence in which a subject lived for 3 or more years.

The information collected was edited and coded in Shenyang and computerized in the United States. Industry and occupation titles were coded according to the system used in the 1982 Population Census of the People's Republic of China. Locations of all Shenyang residences were coded on the basis of their distance and direction from the Shenyang smelter, a major point source of pollution in the city.

Several indices of pollution were created by averaging responses across residences, weighting according to years lived at each. One index represented an average response to the subjective question, "Within a 100-m radius of your residence, how smoky was the outdoor environment? Was it very smoky, somewhat smoky, slightly smoky, or not smoky at all?" Similarly coded variables represented perceived smokiness indoors during the winter and summer. In addition, more objective measures were based on the types of fuels used and location within the home where heating and cooking were carried out. In particular, use of kang was ascertained for each residence. Kang are brick beds under which heated smoke from coal, wood, grass, or other kinds of fuel is passed through pipes before venting to the outside through openings in the sides of the residence. Occasionally, the fuel is burned directly under the bed, which we have designated as "burning kang." In Shenyang and in rural Liaoning, kang are used from October through March to protect against the cold Manchurian winter. For each individual, we evaluated the number of years kang was used, plus the total years of sleeping on kang with fuel burned under the bed. We also calculated an overall indoor air pollution index, P, defined as:

$$P = \sum Y_i (a_i + b_i + c_i) / \sum Y_i$$

where Y_i = years lived at each residence i; $a_i = 0$ if central heat used and 1 otherwise (predominantly coal heat); $b_i = 0$ if the cooking fuel all year was gas, ½ if the cooking fuel in summer only was gas, and 1 otherwise (predominantly coal used all yr); $c_i = 0$ if the cooking place was in a separate kitchen, ½ if the cooking place was in a bedroom or entry corridor in winter, and 1 if the cooking place was in a bedroom or entry corridor all year. Summation was across all residences. The definitions of a_i and b_i were changed slightly if the residence was a rural one, where central heat and gas were rarely used. For rural residences, $a_i = 1$ if the heating system was based on burning kang and 0 otherwise (predominantly kang, but fuel not burned directly under the bed); $b_i = 1$ if the cooking fuel was coal and 0 otherwise (usually dry kindling).

Thus, the index P for each person assumed a value from 0 to 3, with values below 1 indicating potential for relatively low lifetime exposure to indoor air pollution from burning coal.

Food group variables were formed by summing the yearly consumption frequencies of the constituent food items after adjusting for length of season. An index of vitamin A was created by assigning each food item a weight equivalent to its nutrient density (IU of vitamin A/100 g) (5).

Statistical Methods

The statistical analyses were based on multivariate techniques for case-control data (6). Logistic regression analyses were used to estimate summary relative risks (RRs) of lung cancer associated with various factors while adjusting for other factors. The regression models generally contained terms for age, education (no formal education,

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primary or middle school, or high school and higher), smoking (nonsmoker, light, moderate, or heavy smoker), and the indoor air pollution index. We also made additional adjustments for prior history of tuberculosis (yes or no) or chronic bronchitis (yes or no), ever employed in the nonferrous smelting industry (yes or no), the percentage of the subject's life spent in urban areas, and for level of consumption of vitamin A, protein, and other dietary variables. However, these variables had very little effect on the estimates of risks associated with smoking or pollution. Interactions between smoking and pollution indices were evaluated by adding appropriate cross-product terms to the models, with multiple degree-of-freedom significance tested by contrasting likelihoods with and without the cross-product terms included. The regression analyses were run separately for males and females, and also repeated separately for squamous cell or oat cell cancer and adenocarcinoma. Finally, we calculated estimates of population attributable risks (PARs), and associated 95% confidence intervals (CI) as measures of the percentages of lung cancers due to smoking and air pollution (7).

Results

Interviews were completed with 1,249 cancer patients and 1,345 controls. An additional 69 incident lung cancer cases were identified, but 60 had died or were too ill to be interviewed, seven could not be found, and two refused interview, so that the case participation rate was 95%. There were also 64 patients with suspected lung cancer who were excluded from the study when cancer was ruled out by further diagnostic workup. Three eligible controls refused the interview.

The sex and age distributions of the cases and controls were similar (table 1). Fifty-eight percent of the participants were male, with a median age of 59 among males and 56 among females. Most men had at least a primary or middle school education, whereas nearly 50% of the women had no formal education. Among both males and females, the cases tended to be slightly less educated than the controls.

The diagnosis of lung cancer was based on histologic evidence for 83% of the male and 73% of the female cases (table 2). Squamous cell carcinomas accounted for about 50% of the histologically diagnosed cases among men and about 33% among women. Adenocarcinoma was the major cell type among females (38%), compared to 27% among males. Anaplastic small cell (oat cell) carcinomas accounted for 15% of the tumors among males and 17% among females.

Tobacco smoking was reported by 86% of the male and 55% of the female patients. The corresponding percentages among controls (70% and 35%) were significantly lower. **Overall, smoking was associated with a 2.7-fold [95% confidence interval (CI) = 2.1-3.5] increase in lung cancer among males, and a 2.6-fold (95% CI = 2.0-3.3) increase among females after adjusting for age and education.** Among smokers, the median numbers of cigarettes usually smoked per day were 19 and seven for males and females, respectively, and almost all (92%) were current or recent (within the past 5 yr) smokers. For both sexes, the RRs of lung cancer tended to rise with increasing numbers of cigarettes smoked per day and with duration of smoking (table 3). The trends were

Table 1. Percentage distribution of cases and controls by age and education

	Male		Female	
	Case (n = 729)	Control (n = 788)	Case (n = 520)	Control (n = 557)
Age				
30–44	7.4	7.4	7.5	8.8
45–54	20.2	25.1	28.9	28.7
55–59	26.1	22.1	28.7	27.1
60–64	26.6	24.4	21.2	21.0
65–69	19.8	21.1	13.9	14.4
Education				
No formal education	19.2	15.1	51.4	43.8
Primary and junior middle school	65.2	65.8	42.1	45.6
High school and technical institute	9.6	11.3	5.0	6.0
University	5.7	7.7	1.3	2.1

Table 2. Percentage distribution of cases by histologic diagnosis and diagnostic method

	Male	Female
Histologic diagnosis		
Squamous cell carcinoma	42.2 (50.7)*	22.9 (31.5)*
Adenocarcinoma	22.3 (26.8)	27.9 (38.4)
Oat cell carcinoma	12.1 (14.5)	12.5 (17.2)
Large cell carcinoma	1.1 (1.3)	1.2 (1.7)
Others	5.4 (6.5)	8.3 (11.4)
Unknown	16.8	27.3
Diagnostic method		
Pathology	58.4	42.6
Cytology	26.7	32.4
X ray/clinical	14.9	25.0

*Percentage after excluding those with unknown cell type.

Table 3. RRs of lung cancer by cell type associated with intensity and duration of smoking*

Histologic type	Cigarettes/day	Duration of smoking (yr)		
		1–29	30–39	40+
	Males			
All lung cancer	1–19	1.8	2.1	3.3
	20–29	1.5	2.7	6.0
	30+	5.3	4.9	17.1
Squamous cell/oat cell carcinoma	1–19	2.3	2.9	5.0
	20–29	2.6	3.9	10.4
	30+	7.7	8.3	31.2
Adenocarcinoma	1–19	1.4^{ns}	2.2	2.6
	20–29	0.7^{ns}	1.5^{ns}	3.6
	30+	5.4	3.2	11.8
	Females			
All lung cancer	1–19	1.4^{ns}	3.1	3.4
	20+	2.1^{ns}	3.4	9.4
Squamous cell/oat cell carcinoma	1–19	1.8	4.2	5.3
	20+	2.5^{ns}	2.4^{ns}	19.9
Adenocarcinoma	1–19	0.9^{ns}	2.2	1.9
	20+	—	3.7	6.8

*All risks relative to those for nonsmokers and adjusted for age and education. All RRs were statistically significant ($P < .05$) elevated except as noted by "ns" (not significant).

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Table 4. RRs of lung cancer according to home heating and cooking characteristics*

	No. of yr of use	Male			Female		
		Case	Control	RR	Case	Control	RR
Heating method							
Kang (coal)	0	16	20	1.0	4	17	1.0
	1-39	266	336	0.8	164	201	2.4
	40-49	138	135	0.9	65	92	1.9
	50+	307	297	1.0	287	246	3.4†
Burning kang	0	556	667	1.0	415	484	1.0
	1-19	91	68	1.7†	40	38	1.3
	20+	82	53	2.1†	65	35	2.3†
Single standing coal stove	0	60	68	1.0	49	55	1.0
	1-39	440	510	0.8	331	374	0.9
	40-49	140	127	1.0	72	73	0.9
	50+	84	80	1.0	66	53	1.2
Coal stove with pipes extending to other rooms	0	559	642	1.0	401	465	1.0
	1-19	119	121	1.1	81	68	1.4
	20+	48	20	2.3†	35	24	1.5
Central heating (gas)	0	337	370	1.0	312	284	1.0
	1-9	125	110	1.1	68	84	0.8
	10-29	142	192	0.7	85	117	0.7
	30+	85	115	0.8	54	69	0.8
Cooking method and location							
Gas fuel	0	403	396	1.0	304	295	1.0
	1-9	138	159	0.9	99	113	0.9
	10+	188	233	0.8	117	149	0.8
Cooking place in bedroom	0	570	678	1.0	435	503	1.0
	1-29	75	64	1.2	34	25	1.5
	30+	84	46	2.1†	51	29	1.8†

*All RRs adjusted for age, education, and smoking.
†$P < .05$.

stronger for squamous cell and oat cell carcinomas than for adenocarcinoma, with 31-fold (males) and 20-fold (females) excesses of squamous cell and oat cell cancers in long-term heavy smokers. Risks of lung cancer associated with smoking were not modified by diet. Furthermore, no protective effects for retinol and carotene-containing foods were found among smokers or nonsmokers of either sex.

On average, the cases had lived in 3.6 different residences over their lifetimes and the controls in 3.7 (both figures exclude places lived in for <3 yr). The cases spent 62% and the controls 59% of their lifetimes in urban areas. About 75% of all residences were single-story houses.

Table 4 presents risks of lung cancer according to duration of exposure to several types of residential heating and cooking. Nearly all subjects reported having kang in at least one of their homes. Trends in risk with years of living in a house with kang were seen only among females; all RRs were elevated, although only a small number of nonusers of kang were in the baseline reference category. The RRs rose among both sexes; however, when classified by duration of use of burning kang, the RRs reached 1.9 among males and 2.2 among females who reported sleeping on kang with fuel burned directly below the bed for more than 20 years. Risks declined with increasing use of gas (and consequently decreasing use of coal) for both heating and cooking. Risks were also higher when cooking took place in the bedroom or entry corridor to the bedroom than in a separate kitchen or elsewhere in the house.

Table 5 shows the risks associated with ordered categories of the overall indoor air pollution index, P, defined earlier. The RRs tended to rise with increasing indoor air pollution exposure among both males and females. Smoking-adjusted excess risks of 50% or more were reported among the most heavily exposed cases and controls. As shown in table 5, the trends in risk were even more pronounced for squamous cell or oat cell carcinomas. The trends shown in tables 4 and 5 were generally similar in nonsmokers and smokers.

Although most persons reported that their environments were not smoky, more cases than controls reported smoky indoor and outdoor environments (table 6). Compared to groups who reported no smoky environment, twofold increases in lung cancer risk were seen among those who said their neighborhoods were smoky. The excess risks were seen for both squamous cell or oat cell cancers and adenocarcinoma.

Thirty-four percent of the men and 27% of the women in this study reported a factory within 200 m of at least one of their residences (table 7). Based on industrial codes used by the 1982 Chinese Census, we classified the factories into one of 10 specific categories. More cases than controls reported living in a residence within 200 m of any type of factory. Analysis by type of factory revealed that only those living near ferrous or nonferrous metallurgic industries showed significantly elevated risks for both males and females, even after controlling for their years of working in those factories (data not shown). The RRs rose with increased years of living near such factories; RRs reached 2.7 (95% CI = 1.1-6.5) for males and 3.2 (95% CI = 1.0-10.5) for females who lived near the factories for more than 20 years.

We also compared the residential proximity of cases and

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Table 5. RRs of lung cancer according to average indoor air pollution exposure*

Air pollution index, P	Case	Control	All cell types		Squamous cell/oat cell carcinoma		Adenocarcinoma	
			RR	95% CI	RR	95% CI	RR	95% CI
				Males				
0–.9	209	264	1.0	—	1.0	—	1.0	—
1.0–1.4	258	294	1.1	0.8–1.4	1.3	0.9–1.7	1.1	0.7–1.6
1.5–1.9	168	163	1.2	0.9–1.6	1.5	1.0–2.0	1.0	0.6–1.9
2.0+	94	67	1.6	1.1–2.3	1.9	1.0–2.6	1.5	0.9–2.8
				Females				
0–.9	171	217	1.0	—	1.0	—	1.0	—
1.0–1.4	183	193	1.2	0.9–1.6	1.1	0.7–1.7	1.2	0.8–1.9
1.5–1.9	110	104	1.3	0.9–1.9	1.2	0.7–2.0	1.5	0.9–2.4
2.0+	56	43	1.5	1.0–2.4	2.0	1.1–3.6	1.0	0.5–2.2

*All RRs adjusted for age, education, and smoking.

Table 6. RRs of lung cancer associated with perceived smokiness

	Male				Female			
	Case	Control	RR	95% CI	Case	Control	RR	95% CI
Indoor smoke from heating (in winter)								
Not smoky	282	350	1.0*	—	258	329	1.0*	—
Somewhat/slightly smoky	249	259	1.2	1.0–1.5	146	154	1.2	0.9–1.6
Smoky	198	179	1.3	1.0–1.7	116	74	2.0	1.4–2.8
Smoke of outdoor environment								
Not smoky	276	422	1.0†	—	241	342	1.0†	—
Somewhat/slightly smoky	190	190	1.5	1.2–2.0	118	121	1.4	1.1–2.0
Smoky	262	176	2.3	1.7–2.9	161	94	2.5	1.8–3.5

*All RRs adjusted for age, education, and smoking.
†RRs also adjusted for indoor air pollution index P.

Table 7. RRs of lung cancer associated with duration of living within 200 m of industrial factories*

Industrial category of factory	Duration of living (yr)			Percentage of persons reporting factory within 200 m
	0	1–19	20+	
		Males		
Any	1.0	1.3	1.7†	33.6
Electricity, gas production	1.0	0.7	1.7	1.6
Food, tobacco production	1.0	2.4	2.3	4.1
Textiles	1.0	1.1	2.4	2.4
Wood, paper	1.0	0.5	1.8	2.4
Chemical, rubber, drug	1.0	1.5	2.2†	7.9
Cement, glass, asbestos	1.0	3.6†	3.5†	3.0
Ferrous, nonferrous smelter	1.0	1.5	2.7†	4.3
Metal products	1.0	1.2	0.8	6.2
Machinery	1.0	1.2	1.3	17.1
Restaurants	1.0	1.7	2.2	1.8
		Females		
Any	1.0	1.8†	1.6†	26.5
Electricity, gas production	1.0	—	—	0.6
Food, tobacco production	1.0	0.9	0.7	2.6
Textiles	1.0	2.2	0.5	1.8
Wood, paper	1.0	0.6	9.6†	1.7
Chemical, rubber, drug	1.0	2.0	0.9	6.1
Cement, glass, asbestos	1.0	2.1	1.0	2.3
Ferrous, nonferrous smelter	1.0	1.9	3.2†	3.5
Metal products	1.0	4.4†	2.8	4.2
Machinery	1.0	1.9†	1.2	12.5
Restaurants	1.0	4.1	2.8	1.8

*All RRs adjusted for age, education, smoking, and indoor air pollution index P.
†$P < .05$.

controls to the Shenyang nonferrous smelter using street addresses to classify distance. There was an excess of male cases who had lived within 1 km of this particular factory (table 8). The RR associated with having a residence near the smelter was 3.0 (95% CI = 1.5–6.0) after controlling for smoking and working experience in the factory. No excess risk was seen in females or persons of either sex who lived more than 1 km beyond the smelter.

From employment histories recorded during the interviews, the cases and controls had generally similar distributions of work in major industrial and occupational categories, although fewer male cases were ever employed as profes-

Table 8. RRs of lung cancer according to distance of closest residence to the Shenyang smelter

Distance (km)	Case	Control	RR	95% CI
		Males		
<1	35	12	3.0*	1.5–6.0
1.0–1.9	63	79	0.9	0.6–1.3
2.0–2.9	148	169	0.9	0.7–1.2
3.0+	483	525	1.0	—
		Females		
<1	11	10	1.0*	0.4–2.5
1.0–1.9	35	52	0.6	0.4–1.0
2.0–2.9	94	105	0.9	0.6–1.3
3.0+	380	390	1.0	—

*All RRs adjusted for age, education, smoking, and indoor air pollution index P, and relative to risks for those living 3+ km from the smelter.

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Table 9. PAR percentages of lung cancer associated with cigarette smoking and indoor air pollution exposure

Index	All types of lung cancer		Squamous cell/ oat cell carcinoma		Adenocarcinoma	
	PAR	95% CI	PAR	95% CI	PAR	95% CI
			Males			
Smoking*	55	46–65	69	59, 79	38	17, 59
Air pollution† (Index > 1.0)	13	−1, 27	18	2, 34	7	−16, 31
			Females			
Smoking*	37	29, 44	46	34, 57	17	4, 31
Air pollution	17	3, 30	16	−4, 35	12	−10, 34

*PAR of lung cancer associated with smoking after adjusting for air pollution.

†PAR of lung cancer associated with air pollution after adjusting for smoking.

sional or white collar workers. Employment in the nonferrous metal smelting and refining industry (a specific 3-digit manufacturing code) was associated with a smoking-adjusted increased risk of lung cancer among males (RR = 3.6; 95% CI = 1.6–8.2). A total of 26 cases and eight controls were smelter workers. These small numbers hindered evaluation of trends by duration or timing of employment, but most of these men had worked in the smelting industry at least 20 years. Among females, seven cases and five controls (RR = 1.3; 95% CI = 0.4–4.4) had worked in the smelter.

To assess the relative proportions of lung cancers associated with cigarette smoking, air pollution, and occupation in Shenyang, we calculated estimates of PAR. Because only a small number of workers were in the nonferrous smelting industry, less than 4% of the cases among males and 1% among females could be attributed to occupational exposures in smelters. Table 9 lists the PARs associated with smoking and air pollution, using values of the indoor air pollution index, P, less than 1.0 to categorize "nonexposed" and values equal to or greater than 1.0 to categorize "exposed" individuals. As shown, smoking is the dominant cause of lung cancer, accounting for 55% (95% CI = 45%–65%) of the cases among men and 37% (95% CI = 29%–44%) among women. The percentages of squamous cell or oat cell cancers due to smoking were higher, 69% and 46%, respectively, among males and females, than the percentages of adenocarcinoma due to smoking (38% among males and 17% among females). Contributions from air pollution were less, but 13% (−1%–27%) and 17% (3%–30%) of the cases among men and women were associated with high exposure to indoor air pollution.

Discussion

This large population-based case-control study revealed that tobacco smoking is the dominant cause of lung cancer in an area of China where rates are exceptionally high. There were clear trends of increasing risk of lung cancer with rising cigarette consumption, with more than a 25-fold increase in squamous cell or oat cell cancers among heavy smokers. While not surprising to western observers, the findings, when coupled with similar results in Shanghai (*8*), should remove all doubt of whether smoking Chinese cigarettes is harmful. This notion that Chinese cigarettes are not harmful was prevalent throughout China and even among many health professionals at the start of this study. Smoking also appears to account for at least part of the geographic gradient in lung cancer mortality in China, where high rates among females cluster in the northern provinces (*2*). Among women in our control series, 35% had smoked cigarettes, a figure nearly double that reported among females of similar age in Shanghai and elsewhere in China (*8,9*). We did not observe expected protective effects for frequent consumption of either beta-carotene or retinol, and risks associated with smoking did not vary with diet.

The primary contribution of this study, however, may be its ability to examine risks of lung cancer associated with pollution from industrial and domestic sources. Shenyang is anecdotally said to have among the highest levels of air pollution in the world, even though there are fewer automobiles than in western cities. Pollution results mainly from industrial emissions and from combustion of fuel (mostly coal) for home heating and cooking. Shenyang is a densely populated city (2,700,000 persons in 164 km^2), with most people traditionally living in close quarters in single-story dwellings heated by kang. We measured wintertime benzo(*a*)pyrene concentrations in and around 10 single-story homes, 10 two-story homes, and 10 apartment buildings three or more stories tall. There was little variation in outdoor levels by housing type. Average concentration was around 60 ng/m^3 in January, a level 60 times higher than the recommended upper limit for U.S. urban air (*10*). Inside, however, average levels differed according to structure. The level was highest (and exceeded outdoor levels) for traditional single-story homes, declined slightly in two-story homes, and dropped by more than 50% in high-rise apartment buildings.

We found significant associations between lung cancer risk and measures of indoor air pollution, despite the relative crudeness of the pollution indices used and the likely misclassification of exposure that would have dampened RR estimates. Risks were 50%–70% higher among those who spent most of their lives living in homes heated by coal and using coal as the primary cooking fuel. Although most homes had kang, persons who slept on kang in which fuel was directly burned, and those who cooked in their sleeping quarters, had higher risks of lung cancer than those who did not. These measures of pollution were created from responses to questions that should be objectively answered (i.e., questions on types of heating and cooking facilities), and risk patterns based on these measures correlated well with patterns derived from subjective appraisals of house and neighborhood smokiness. It is noteworthy that the effects of indoor air pollution were stronger for squamous cell and oat cell cancers than for adenocarcinoma, thus paralleling the effects of cigarette smoking.

The link between coal burning and lung cancer in Shenyang is qualitatively similar to that observed in a high-risk area of Yunnan province in south China, where living in houses without chimneys that are heated by soft lo-

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cal coal was found to contribute more than cigarette smoking to the elevated rates of lung cancer in women (*11*). In western countries, the effects of air pollution on lung cancer risk have been more difficult to identify and disentangle from the effects of smoking and occupational exposure (*10–12*). In Shenyang, the high levels of air pollution provide a wider range of exposure over which to evaluate dose-response trends with lung cancer, after adjustment for smoking and other risk factors. Our conclusion is that the concentrated use of coal-burning stoves in Shenyang is a likely cause of lung cancer in the area, and perhaps 10%–20% of the cases are related to pollution.

This study also evaluated risks associated with a particular point source of pollution, i.e., the Shenyang smelter, which has released inorganic arsenic and other metals. Workers in the nonferrous smelting industry were found to have a threefold increased risk of lung cancer, similar to workers who are exposed to inorganic arsenic in U.S. copper smelters (*13,14*). We plotted residences according to distance from the smelter's central stacks and found more cases than controls among men living within 1 km. The resultant excess risk among males was not accounted for by employment in the industry or smoking. As part of the investigation, we obtained soil samples at varying distances from the smelter. Assays of metals, including inorganic arsenic, revealed a rapid drop as distance from the smelter increased; the highest levels were within 1 km. Thus, similar to other areas of the world (*15–18*), particulate smelter emissions in Shenyang have been detected in the surrounding neighborhood. However, the excess risk of lung cancer among those who lived near the smelter was observed in males but not in females. Therefore, we cannot definitively confirm reports of higher lung cancer risk among residents living in the vicinity of smelters in the United States and Sweden (*18–21*), despite the large numbers of persons living within a few kilometers of the Shenyang smelter.

A recently completed investigation of lung cancer in Shanghai suggested that another form of indoor pollution, namely, prolonged exposure to oil volatiles from cooking with a wok at high temperature, may be related to increased risk of both squamous cell carcinoma and adenocarcinoma of the lung (*22*). Risks among Shanghai women rose with the frequency of wok cooking, with reported smokiness of the house, and with reported eye irritation during cooking. The risks were most pronounced when exposure to rapeseed oil fumes was involved. Although we also found similar trends for some of these variables, we could not adequately examine these hypotheses, because our questionnaire did not include an extensive cooking method section and rapeseed oil was rarely used in Shenyang. Conversely, the Shanghai study could not evaluate lung cancer risks from kang or other heating exposure, since less than 5% of the homes in Shanghai were heated.

In summary, this large population-based case-control study has confirmed that cigarette smoking is the major determinant of lung cancer in Shenyang, as it is elsewhere in the world. High levels of indoor air pollution from coal-burning stoves also appear to contribute, and they combine with an elevated frequency of smoking to account for the high rates of lung cancer among women in northeast China.

References

(*1*) National Cancer Control Office: Atlas of Cancer Mortality in the People's Republic of China. Beijing: China Map Press, 1980

(*2*) Xu ZY, Blot WJ, Fraumeni JF Jr: Geographic variation in female lung cancer in China. Am J Public Health 76:1249–1250, 1986

(*3*) Waterhouse J, Muir C, Shanmugaratnam K, et al: Cancer Incidence in Five Continents, vol IV. Lyon: IARC, 1982

(*4*) Xiao H, Xu ZY: Air pollution and lung cancer in Liaoning Province, People's Republic of China. Natl Cancer Inst Monogr 69:53–58, 1985

(*5*) Ershow AG, Chen WK: Chinese food composition tables: A translation with English common names, Latin scientific names, and Pinyin romanized transliterations. Food Comp Anal. In press

(*6*) Breslow NE, Day NE: Statistical methods in cancer research. Volume I—the analysis of case-control studies. IARC Sci Publ 32:5–338, 1980

(*7*) Whittemore AS: Estimating attributable risks from case-control studies. Am J Epidemiol 117:76–85, 1983

(*8*) Gao YI, Blot WJ, Zheng W, et al: Lung cancer and smoking in Shanghai. Int J Epidemiol 17:277–280, 1988

(*9*) Weng XZ, Hong ZG, Chen DY: Smoking prevalence in Chinese aged 15 and above. Chin Med J 100:886–892, 1987

(*10*) Shy CM, Struba RJ: Air and water pollution. *In* Cancer Epidemiology and Prevention (Schottenfeld D, Fraumeni JF Jr, eds). Philadelphia: Saunders, 1982, pp 336–363

(*11*) Mumford JL, He XZ, Chapman RS, et al: Lung cancer and indoor air pollution in Xuan Wei, China. Science 235:217–220, 1987

(*12*) Doll R, Peto R: The causes of cancer. Quantitative estimates of avoidable risks of cancer in the United States. JNCI 66:1191–1308, 1981

(*13*) Lubin JH, Pottern LM, Blot WJ, et al: Respiratory cancer among copper smelter workers: Recent mortality statistics. J Occup Med 23:779–784, 1981

(*14*) Enterline PE, Henderson VL, Marsh GM: Exposure to arsenic and respiratory cancer: A re-analysis. Am J Epidemiol 125:929–938, 1986

(*15*) Hartwell TD, Hardy RW, Harris BS, et al: Heavy metal exposure in populations living around zinc and copper smelters. Arch Environ Health 38:284–295, 1983

(*16*) Baker EL, Hayes CG, Landrigan PJ, et al: A nationwide survey of heavy metal absorption in children living near primary copper, lead, and zinc smelters. Am J Epidemiol 106:267–273, 1977

(*17*) Milham S, Strong T: Human arsenic exposure in relation to a copper smelter. Environ Res 7:176–182, 1974

(*18*) Pershagen G: Lung cancer mortality among men living near an arsenic-emitting smelter. Am J Epidemiol 122:684–694, 1985

(*19*) Frost F, Harter L, Milham S, et al: Lung cancer among women residing close to an arsenic emitting copper smelter. Arch Environ Health 42:148–152, 1987

(*20*) Brown LM, Pottern LM, Blot WJ: Lung cancer in relation to environmental pollutants emitted from industrial sources. Environ Res 34:250–261, 1984

(*21*) Greaves WW, Rom WN, Lyon JL, et al: Relationship between lung cancer and distance of residence from nonferrous smelter stack effluent. Am J Ind Med 2:15–23, 1981

(*22*) Gao YT, Blot WJ, Zheng W, et al: Lung cancer among Chinese women. Int J Cancer 40:604–609, 1987

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A Case-Control Study of Lung Cancer in Nonsmoking Women

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*Department of Public Health, Tohoku University School of Medicine, Sendai 980, *the Second Department of Internal Medicine, Nagoya City University, Medical School, Nagoya 467, †the Third Department of Internal Medicine, Aichi Medical University, Aichi 480-11, ‡Department of Internal Medicine, National Nagoya Hospital, Nagoya 460, §Department of Internal Medicine, Aichi Cancer Center Hospital, Nagoya 464, ‖Department of Surgery, Aichi Cancer Center Hospital, Nagoya 464, ¶Department of Internal Medicine, Chukyo Hospital, Nagoya 457 and **Division of Epidemiology, Aichi Cancer Center Research Institute, Nagoya 464*

SHIMIZU, H., MORISHITA, M., MIZUNO, K., MASUDA, T., OGURA, Y., SANTO, M., NISHIMURA, M., KUNISHIMA, K., KARASAWA, K., NISHIWAKI, K., YAMAMOTO, M., HISAMICHI, S. and TOMINAGA, S. *A Case-Control Study of Lung Cancer in Nonsmoking Women*. Tohoku J. exp. Med., 1988, 154 (4), 389-397 —— A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated relative risk (RR) of lung cancer was observed for passive smoking from mother (RR = 4.0; $p < 0.05$) and from husband's father (RR = 3.2; $p < 0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR = 4.8; $p < 0.05$). No appreciable differences in food intakes were observed between cases and controls. ——— lung cancer; women; nonsmoker; passive smoking; metal exposure

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The causes of lung cancer in Japanese women have not been clearly identified. It is widely accepted that cigarette smoking is causally associated with lung cancer, but the increasing trend in the incidence of lung cancer in Japanese women cannot be explained by smoking alone. The proportion of smokers among Japanese women remained around 15% during the last thirty years (Tominaga 1982) and the most predominant histologic type of lung cancer among them was adenocarcinoma, which was considered to be more weakly associated with smoking as compared to lung cancer of other cell types (Shimizu 1983; Nakamura et al. 1986; Shimizu et al. 1986).

Several studies have been conducted with emphasis laid on passive smoking and lung cancer since the first positive results were presented by Hirayama (1981) and Trichopoulos et al. (1981). Some of these studies showed a clear association of passive smoking with lung cancer (Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986; Inoue et al. 1986). However, the results of other studies were equivocal or negative (Garfinkel 1981; Kabat and Wynder 1984; Koo et al. 1984; Wu et al. 1985; Lee et al. 1986).

This paper reports a case-control study of lung cancer in Japanese nonsmoking women, in which passive smoking and other factors such as occupational history, domestic heating system and dietary habits were investigated.

Materials and Methods

Our cases consisted of female patients with primary lung cancer who were treated in 4 hospitals in Nagoya from August 1982 to July 1985. One of the hospitals (Aichi Cancer Center Hospital) was a cancer hospital and the remaining three were general hospitals. Nagoya is the fourth largest city in Japan with a population of 2.1 million and located in the middle of the main island, Honshu.

During the above period 118 female lung cancer patients were pathologically identified. The physicians or nurses asked all of them to fill in a questionnaire for this study on the first or second day of admission to the hospitals. Out of 118 lung cancer patients 4 refused to fill in the questionnaire and 24 reported that they were current or exsmokers. The remaining 90 nonsmoking patients were selected as the cases for the following analyses. The questionnaire mainly consisted of the questions about smoking, occupational history, dietary habits, personal disease history and about the kinds of fuel for cooking. As regards passive smoking, we asked them about the smoking habits or the number of cigarettes smoked per day by parents, siblings, children or husband's parents in the home. We also asked them about the length of time which the woman spent with her husband in the same room, the period of married life and the number of cigarettes smoked by her husband. The passive smoke exposure at working places was assessed only in terms of the presence or absence of smokers. As regards dietary history, we asked the frequency in recent five years of intake of food items and divided into four categories (no intake, 1 or 2 days/week, 3 or 4 days/week, and almost every day). We asked directly the number of glasses of milk and the number of oranges taken per week.

The 90 lung cancers included 69 adenocarcinomas (77%), 13 spuamous cell carcinomas (14%), 4 large cell carcinomas (4%), 3 small cell carcinoma (3%) and 1 adenoid cystic carcinoma (1%). The number of cases in the age group of 30-39, 40-49, 50-59, 60-69, 70-79 and 80+years were 3 (3%), 16 (17%), 28 (31%), 27 (30%), 14 (16%) and 2 (2%) respectively. The minimum and maximum ages of the cases were 35 and 81 years and those

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of controls were also 35 and 81 years, respectively. The mean age at admission was 59 years for cases and 58 years for controls.

As a control, we asked female in-patients other than those with lung cancer in the same or adjacent wards of the hospital to fill in the questionnaire as we did for lung cancer patients (i.e., potential controls). We selected two controls matched in terms of hospital (the same hospital), age (±1 year), and date of admission for each case from these potential controls. For 17 cases we could find only one control which satisfied the criteria. The controls finally used for this analysis comprised 163 patients with the following diseases: breast cancer 67, (41%); diabetes mellitus, 11 (7%); stomach cancer, 11 (7%); hepatitis and other liver diseases, 8 (5%); malignant lymphoma, 7 (4%); heart diseases 5, (3%); hypertension 5, (3%); gall stone, 4 (2%); colorectal cancer 3, (2%); cancer of the uterine cervix 3, (2%); and others 39, (24%).

The logistic regression method was applied to this individually matched case-control study and odds ratio was computed as estimated relative risk for each variable (Breslow et al. 1978; Breslow and Day 1980). The statistical significance was determined by using two-sided p values.

Results

Table 1 shows the risk of female lung cancer for several types of passive smoking. When the mother of a case was a smoker, the relative risk of lung cancer was 4.0 ($p<0.05$). However, the risk was not elevated when her father was a smoker (RR = 1.1). High relative risk was observed when the husband's father living with the case smoked in the home (RR = 3.2; $p<0.05$). When mother or husband's father was a smoker, the relative risk was 3.3 ($p<0.01$). There was no association between the risk of lung cancer and smoking by husband, siblings or children in the home.

Passive smoke exposure at work was not clearly associated with female lung cancer, although the relative risk was slightly elevated (RR = 1.2).

Table 2 shows the combined effect of household smoking by mother and

Table 1. *Relative risks (RR) of lung cancer in nonsmoking women for several types of tobacco smoke exposure*

Smoker	Frequency in controls (%)	RR
In the home:		
Husband	56	1.1
Father	41	1.1
Mother	3	4.0*
Husband's father	8	3.2*
Husband's mother	4	0.8
Son(s) or daughter(s)	40	0.8
Brother(s) or sister(s)	32	0.8
Someone at working place	35	1.2

*$p<0.05$.

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TABLE 2. *Relative risks of lung cancer in nonsmoking women for smoking by mother and husband's father in the home*

		Smoking by husband's father	
		(−)	(+)
Smoking by mother	(−)	1.0	3.9*
	(+)	6.3	2.8

*$p < 0.05$

husband's father. Both of these two variables showed a relatively high risk independently. Particularly, the risk for smoking by husband's father in the absence of smoking by mother was significantly elevated (RR = 3.9, $p < 0.05$). However, no synergistic effect of the above two variables was observed.

About 60% of the respondents had occupations. No difference was found in the distribution of the occupational categories between cases and controls. However, histories of occupational exposure to specific substances showed high risks of lung cancer. The relative risk for exposure to iron or other metals was 4.8 ($p < 0.05$), although the frequency of such exposure was very low in controls. The relative risk for exposure to coal, stone, cement, asbestos or ceramics was 3.3, but it was not statistically significant.

For the analysis of dietary habits, cut points dividing into lower two and higher two categories are arbitrarily chosen in general. We selected the 8/week or more as cutpoint for mandarine oranges in winter and odds ratio of milk was computed for the daily intake. Table 3 shows that there is neither positive nor negative association with food items investigated here. Only chicken showed the low risk of 0.7. We observed no dose-response relationship for these variables.

The personal medical history of silicosis showed the relataive risk of 2.0, but

TABLE 3. *Relative risks (RR) of lung cancer in nonsmoking women in relation to the frequency of food intake*

Food item	Frequency of intake	Frequency of intake in controls (%)	RR
Green-yellow vegetables	≥3 d/w	86	0.9
Fruit	≥3 d/w	86	1.2
Oranges (mandarine)	≥8/w	77	1.0
Milk	≥1 glass/d	76	1.0
Fish	≥3 d/w	55	1.0
Pork	≥3 d/w	22	1.0
Beef	≥3 d/w	20	1.0
Chicken	≥3 d/w	40	0.7

d: days; w: weeks.

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TABLE 4. *Relative risks (RR) of lung cancer in nonsmoking women for type of household heating system used in recent years*

Type of household heating system	Frequency in controls (%)	RR
Gas	32	1.0
Kerosene	86	1.6
Coal or charcoal	8	1.7

TABLE 5. *Relative risks (RR) of lung cancer in nonsmoking women in relation to the selected factors (n = 65)*

Factor	RR	
	Crude	Adjusted†
Smoking by mother in the home	3.0	2.1
Smoking by husband's father in the home	3.5*	3.2*
Occupational exposure to iron or other metals	2.8	2.4

†RR of each factor adjusted for other two factors after excluding the pairs in which one of the factors had unknown values.

*$p < 0.05$.

it was not statistically significant. The risk for histories of both chronic bronchitis and asthma was 0.8, and the risk for history of tuberculosis was 1.1.

No appreciable difference was observed between cases and controls in the type of household heating in childhood and in the kinds of fuel for cooking in adulthood. However, a recent use of a kerosene or coal (charcoal) stove for household heating showed a somewhat higher risk (RR = 1.6 and 1.7, respectively). However, neither of them was statistically significant (Table 4).

The frequency of using cooking oil was almost the same in cases and controls.

To confirm the risk associated with each variable described above, we computed the relative risk by using the multiple logistic regression analysis for the main 3 variables. Table 5 shows that the results are almost the same as those in univariate analysis.

Discussion

The presence of a smoking family member does not necessarily indicate that exposure to a sidestream of cigarettes has actually occurred. To know the level of passive smoking, measurement of concentration of cotinine in the urine is useful (Matsukura et al. 1984; Wald et al. 1984). However, it is very hard to assess the passive smoking level over a period of several decades because the half-life of serum cotinine is 72 hr. In this analysis we used only the information on smoking history of the respondents, their family members and their colleagues at working

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places.

In this study we found a positive association between lung cancer in nonsmoking women and the smoking history of family members, especially that of mother and husband's father. As Japanese children usually spend much longer time with their mother than other family members do, mother's smoking may be a representative index of passive smoking before leaving home at around 20 years of age. Recently we found that the saliva cotinine level of nonsmoking schoolchildren is not high when their fathers were smokers but high when their mothers were smokers in Miyagi, a district of northeastern Japan (unpublished data). After marriage, 35% of women in controls lived with their husband's parents. The final proportion of control women whose husband's father smoked cigarettes in the home was as small as 8%, but that (18%) of cases was somewhat larger. The husband's father may have retired already and may have stayed home much longer than the husbands. There is a possibility that Japanese women may be more frequently exposed to the smoke of cigarettes by their husband's father than that by their husband.

We assessed the total length of period which a woman spent with her husband from the length of the period of marriage and the hours during which she lived in the same room, but no difference was found between cases and controls.

No dose-response relationship was observed between the risk of lung cancer and the history of smoking of mother or husband's father. Usually the respondents remember whether their mother or their husband's father were smokers, but they may be unable to recall the exact number of cigarettes smoked by their mother (especially in childhood) or husband's father in the home.

It has been suggested that beta-carotene and preformed vitamin A decrease the risk of lung cancer (Smith 1982 ; Hinds et al. 1984). We asked a very simple question concerning the frequency of green-yellow vegetable intake, which has been referred to as a protective factor against lung cancer in a large cohort study of Japan (Hirayama 1982). No association was observed between this variable and female lung cancer risk in our study. Most of the respondents had green-yellow vegetables very frequently and we found no difference between cases and controls. There was no dose-response relationship between the frequency of intake of green-yellow vegetables and lung cancer risk.

We also assessed the efficacy of vitamin supplements over a period of more than one year in this analysis, and found the risk of 0.5. However it was not statistically significant.

Other dietay factor such as vitamin C and cholesterol may be related to the development of lung cancer (Hinds et al. 1983, 1984 ; Byers and Graham 1984), but no appreciable association was observed between the risk of lung cancer and the intake of food items listed in this study. To evaluate the effect of dietary habits, more precise measurement of food intake is needed.

A slightly elevated risk for disease history of silicosis is consistent with the

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data in recent reports (Finkelstein et al. 1982; Lynge et al. 1986), despite the fact that our results were based on the information reported by the respondents and that the number of cases with silicosis was very small. An excess risk of adenocarcinoma of the lung was observed previously for those with occupational exposure to iron or other metals in Nagoya area (Shimizu 1983). Even if the risk for these occupational exposure is confirmed, contribution of these factors is small because the frequency of such exposure is very low in Japan.

Possibly there is some bias in our study. Lung cancer cases were not derived from general population but from the patients of a limited number of hospitals. The proportion of adenocarcinoma patients in our series was ten percent larger as compared with that in total lung cancer patients of this area. The proportion of squamous cell carcinoma showed an opposite tendency (Karasawa 1985). We selected the controls from the same hospitals considering that both cases and controls in the same hospital may have similar backgrounds. However, one of the hospital was a cancer hospital and we had to include many breast cancer patients in the controls. For this reason we compared the status of passive smoking among the breast cancer patients with that among other controls, but we found no difference. Furthermore, the risk of lung cancer for the survivors of cancer of the breast was not high when assessed by the data of a population-based cancer registry (Takano and Okuno; personal communication).

Our study showed that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. As the precise situation of passive smoking in the home or other places is still unclear, further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

Acknowledgments

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References

1) Akiba, S., Kato, H. & Blot, W.J. (1986) Passive smoking and lung cancer among Japanese women. *Cancer Res.*, 46, 4804-4807.
2) Breslow, N.E. & Day, N.E. (1980) The analysis of case-control studies. In: *Statistical Methods in Cancer Research*, Vol. 1. IARC Scientific Publications No. 32. International Agency for Research on Cancer, Lyon.
3) Breslow, N.E., Day, N.E., Halvorsen, K.T., Prentice, R.L. & Sabai, C. (1978) Estimation of multiple relative risk functions in matched case-control studies. *Amer. J. Epidemiol.*, 108, 299-307.
4) Byers, T. & Graham, S. (1984) The epidemiology of diet and cancer. In: *Advances in Cancer Research*, Vol. 41, edited by G. Klein & S. Weinhouse, Academic Press, Orlando-Florida, pp. 1-69.
5) Correa, P., Pickle, L.W., Fontham, E., Lin, Y. & Haenszel, W. (1983) Passive

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smoking and lung cancer. *Lancet*, 2, 595-597.
6) Finkelstein, M., Kusiak, R. & Suranyi, G. (1982) Mortality among miners receiving workmen's compensation for silicosis in Ontario: 1940-1975. *J. occup. Med.*, 24, 663-667.
7) Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J. nat. Cancer Inst.*, 66, 1061-1066.
8) Garfinkel, L., Auerbach, O. & Joubert, L. (1985) Involuntary smoking and lung cancer: A case-control study. *J. nat. Cancer Inst.*, 75, 463-469.
9) Hinds, M.W., Kolonel, L.N., Hankin, J.H. & Lee, J. (1983) Dietary cholesterol and lung cancer risk in a multiethnic population in Hawaii. *Int. J. Cancer*, 32, 727-732.
10) Hinds, M.W., Kolonel, L.N., Hankin, J.H. & Lee, J. (1984) Dietary vitamin A, carotene, vitamin C and risk of lung cancer in Hawaii. *Amer. J. Epidemiol.*, 119, 227-237.
11) Hirayama, T. (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Brit. med. J.*, 282, 183-185.
12) Hirayama, T. (1982) Epidemiological aspects of lung cancer in the Orient. In: *Lung Cancer 1982*, edited by S. Ishikawa, Y. Hayama & K. Suemasu. Excerpta Medica, Amsterdam-Oxford-Princeton, pp. 1-13.
13) Inoue, R., Ohtsuka, T., Shimura, K. & Hirayama, T. (1986) A case-control study of lung cancer. *Lung Cancer*, 26, 763-767. (Japanese)
14) Kabat, G.C. & Wynder, E.L. (1984) Lung cancer in nonsmokers. *Cancer*, 53, 1214-1221.
15) Karasawa, K. (1985) Distribution of histological types of lung cancer in Aichi Prefecture. *Jap. J. Chest Dis.*, 44, 809-813. (Japanese)
16) Koo, L.C., Ho, J.H. & Saw, D. (1984) Is passive smoking an added risk factor for lung cancer in Chinese women. *J. exp. clin. Cancer Res.*, 3, 277-283.
17) Lee, P.N., Chamberlain, J. & Alderson, M.R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Brit. J. Cancer*, 54, 97-105.
18) Lynge, E., Kurppa, K., Kristoferson, L., Malker, H. & Sauli, H. (1986) Silica dust and lung cancer: Results from the Nordic occupational mortality and cancer incidence registers. *J. nat. Cancer Inst.*, 77, 883-889.
19) Matsukura, S., Tominato, T., Kitano, N., Seino, Y., Hamada, H., Uchibashi, M., Nakajima, H. & Hirata, Y. (1984) Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers. Evidence for passive smoking. *New Engl. J. Med.*, 311, 828-832.
20) Nakamura, M., Hanai, A., Fujimoto, I., Matsuda, M. & Tateishi, R. (1986) Relationship between smoking and the four major histologic types of lung cancer. *Lung Cancer*, 26, 137-148. (Japanese)
21) Shimizu, H. (1983) A case-control study of lung cancer by histologic type. *Lung Cancer*, 23, 127-137. (Japanese)
22) Shimizu, H., Hisamichi, S., Motomiya, M., Oizumi, K., Konno, K., Hashimoto, K. & Nakada, T. (1986) Risk of lung cancer by histologic type among smokers in Miyagi Prefecture. *Jap. J. clin. Oncol.*, 16, 117-121.
23) Smith, A.H. (1982) Relationship between vitamin A and lung cancer. *Nat. Cancer Inst. Monogr.*, 62, 165-166.
24) Tominaga, S. (1982) Smoking in Japan. In: *The UICC Smoking Control Workshop*, edited by S. Tominaga & K. Aoki, University of Nagoya Press, Nagoya, pp. 27-35.
25) Trichopoulos, D., Kalandidi, A., Sparros, L. & MacMahon, B. (1981) Lung cancer and passive smoking. *Int. J. Cancer*, 27, 1-4.
26) Wald, N.J., Boreham, J., Bailey, A., Ritchie, C., Haddow, J.E. & Knight, G. (1984) Urinary cotinine as marker of breathing other people's tobacco smoke. *Lancet*, 1,

2023381759

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230–231.

27) Wu, A.H., Henderson, B.E., Pike, M.C. & Yu, M.C. (1985) Smoking and other risk factors for lung cancer in women. *J. nat. Cancer Inst.*, **74**, 747–751

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PASSIVE SMOKING AMONG NONSMOKING WOMEN AND THE RELATIONSHIP BETWEEN INDOOR AIR POLLUTION AND LUNG CANCER INCIDENCE--RESULTS OF A MULTICENTER CASE CONTROLLED STUDY. Gan to Rinsho, Vol. 36, No. 3, pp.329-333. 1990.

Introduction

According to the 1987 population dynamics statistics compiled by the Ministry of Health and Welfare, the age-adjusted mortality of lung cancer in both men and women is the second highest (after stomach cancer) among cancer mortalities[1]. The age-adjusted mortality in stomach cancer has been steadily declining since 1960, while that of lung cancer has been rapidly increasing during the same period. If this trend continues, the ranking of these mortalities will be reversed by the year 2000[2].

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For risk factors to explain this rising incidence of lung cancer, smoking is cited first. In Japan, the incidence of smoking among men has been declining in recent years but it was reported to be 55% in 1988[3], a rate considerably higher in comparison to the incidences in the western world. Thus the promotion of an antismoking policy is considered to be necessary. Although the incidence of smoking has recently been increasing among young women, it was reported to be mere a 9%[3] in 1988, a figure much lower than those in western societies. To reflect this situation, the population-attributable risk of lung cancer due to smoking is 71% in men and only 26% in women[4]. In other words, it is suggested that risk factors other than smoking exist in the development of lung cancer among women.

In the past, for risk factors other than smoking that cause lung cancer to develop, studies have been conducted with a major focus on occupational exposure. In women, however, it is necessary that studies on exposure to various elements in the everyday environment supersede the investigation of the effects of occupational factors. However the relative risk of these elements in everyday environment is expected to be comparatively small. Thus it is necessary to include as many cases of lung cancer among nonsmoking women as possible for the analysis.

The purpose of the present study is to elucidate the risk factors of lung cancer among nonsmoking women. Therefore the status of passive smoking and the relationship between indoor air pollution and the development of lung cancer were investigated, using the data from the case-controlled studies conducted jointly by a number of health facilities. It should be noted that the study uses data collected up to the end of March 1989; thus the figures may be different in the final section of the report which is scheduled for the coming year.

1. Subjects and Method.

The "Organization to Eliminate Lung Cancer from Osaka"[3], with the participation of 8 major hospitals in Osaka specializing in the treatment of lung cancer, has been conducting a hospital-based case-controlled study since January 1986. Among the

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patients newly admitted with a diagnosis of primary lung cancer, 658 men and 193 women were registered by the end of March 1989. Only 23 out of these 658 men (3.5%) were lifetime nonsmokers. Among the 193 female patients, however, 120 (62%) were nonsmokers. The present analysis was limited to these nonsmoking female patients. Of the lung cancers in these nonsmoking women, 78% were classified as adenocarcinoma.

For control, 519 nonsmoking female patients were selected from those newly admitted to the same hospitals with a diagnosis other than lung cancer. Neoplastic diseases were the predominant diagnosis (85%) of these patients. Breast cancer (240 cases) was the most common, followed by stomach cancer (63 cases). For the analysis, the ages criteria at the time of admission was set from 40 to 79 years for both the lung cancer patients and control.

The information on smoking and indoor air pollution was obtained from a questionnaire, filled out by the patients, which was distributed and collected at the time of admission. Any questionable responses concerning the present analysis were excluded from tabulation. Medical information such as histological type of cancer was obtained from attending physicians. The age-adjusted odds ratio and 95% confidence level were computed by the Mantel-Haenszel method using the PROC FREQ of SAS[6]. Factors with an estimated value of the odds ratio over 1.5 or below 0.67 were selected and subjected to a logistic regression analysis using PROC LOGIST of SAS[7].

2. Results

Table 1 shows an age-adjusted odds ratio where the population was divided into those with smoking husbands and other members of the family who were smokers. The table was prepared to find the effects of passive smoking on lung cancer in adults (prior to hospital admission). The odds ratio when the husbands were smokers was almost 1 (0.94), while smoking by other members in the household raised it to 1.45, indicating a slight increase in risk. Most of the other smoking members in a household were children.

To find the effects of passive smoking during early

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childhood, the age-adjusted odds ratios were computed when fathers, mothers, or other members of the household were smokers. The results are shown in Table 2. When fathers were smokers, the odds ratio of passive smoking was 0.60, with a significant reduction in risk. When mothers were smokers, the odds ratio was computed to be 1.71. The risk rose in this instance but the change was not significant. The odds ratio for smoking by other members of the families was computed to be 1.13.

Table 3 shows the effects of using room heaters (which may be a cause of indoor air pollution) on the development of lung cancer as an age-adjusted odds ratio. The ratio was computed separately for each age category when the heater was in use. For heating facilities which may be the cause of indoor air pollution the following were included: unvented stoves using gasoline, gas, coal, charcoal briquettes, or wood; or a brazier, clay charcoal stove, or foot warmer which burns charcoal or briquettes. Air conditioners, stoves with vents, electric stoves, and electric foot warmers were excluded from the study. Odds ratios were computed in relation to the use of these sources of pollution at each age level when the heaters were used. As shown in Table 3, the ratios were near 1 for each age level, showing no significant relationship.

The effects of using foot warmers (burning charcoal, small briquettes, or round briquettes for the source of heat when sleeping) on the incidence of lung cancer were studied and expressed as an age-adjusted odds ratio in Table 4. These ratios, shown by age level, were near 1 for all ages, indicating no significant relationship.

Next, age-adjusted odds ratios were computed for the effects of using straw or wood for cooking on the development of lung cancer (Table 5). Again, the ratios were computed for each group. The ratio was 1.33 when the fuel was used at age 15 and 1.90 when used at age 30, with the latter showing a statistical significance. All the patients who had been using straw or wood for cooking at age 30 had also used the same fuel at age 15. Therefore the odds ratio computed at age 30 was interpreted to

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express the effect of long-term exposure to this source of pollution. None of the patients was still using straw or wood as a source of cooking heat.

In these analyses, the odds ratios for the following 3 situations were computed to be over 1.5 or less than 0.67: smoking by father or mother when the patient was young and the use of straw or wood as the source of cooking heat at age 30. Using these 3 situations as variables, the odds ratio was estimated using a logistic regression model (Table 6). It was found that only the use of straw or wood as the source of cooking heat at age 30 showed a statistical significance.

3. Discussion

The results of the present study suggested that the use of straw or wood as a cooking fuel in the past is a risk factor in the development of lung cancer among nonsmoking women. Gao, et al.[9] investigated women in Shanghai and reported that the use of rapeseed oil raises the risk of lung cancer by 40%. In the same report, the use of cooking fuel (coal, city gas, and wood) did not increase the risk. Koo, et al.[8] conducted a study on women residing in Hong Kong and reported that among cooking fuels, the use of petroleum increases the risk of lung cancer while the risk is lower when propane gas (LPG) is used. However they added that these effects are relatively insignificant. MacLennan, et al.[10] conducted a study on Chinese women in Singapore and reported that there was no difference with respect to the risk of lung cancer when wood or charcoal used as cooking fuel was compared against petroleum and gas. The subjects of these studies were all Chinese women. In addition, exposure was based on whether the subjects ever used the fuel in question at all in the past or whether they are currently using it. Such criteria may not necessarily reflect past exposure accurately. Furthermore there is a possibility that those who were classified as "not exposed" may actually have been substantially exposed. If these possibilities are taken into consideration, the results of these studies do not necessarily contradict ours.

No subjects currently use straw or wood for cooking fuel so

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we could not institute a policy of primary prevention of lung cancer in relation to this practice. However the finding is considered significant in suggesting that some factor(s) closely related to our daily lives may be recognized as risk factor(s) for lung cancer that appears 10 or 20 years later.

No statistical significance was obtained from the effect of maternal smoking when the subjects were young. However the estimated odds ratio was high (1.79) and the power to detect the significant difference from the cases of the present study was computed to be 56%. Therefore further studies with a larger number of subjects are considered necessary. As for the short-term effect of maternal smoking on the health of children, Tager, et al.[11] reported that the respiratory function was depressed in children when parents were smokers and the tendency was exaggerated when the mothers were smokers. Wu, et al.[12] conducted a case-controlled study on white women in Los Angeles but they failed to find a significant relationship between lung cancer and maternal smoking. In Japan, Shimizu, et al.[13] reported an odds ratio of 1.6 for maternal smoking in relation to lung cancer in women.

In the present study, the risk of lung cancer from paternal smoking was significantly reduced in a single variate analysis but the results of a multivariate analysis were not significant. Compared with the mother, the time a child spends with her father is expected to be short; and the tendency towards a decline in risk is believed to be due to some confounding factor (such as social class).

For the effect of passive smoking during adulthood, the present study focused on smoking by husbands but no significant correlation with lung cancer was established. In Japan, Hirayama[14], and Akiba, et al[15] found a significnat relationship between the two but Shimizu, et al.[13] did not. Blot, et al.[16] conducted a meta analysis based on epidemiological data throughout the world and estimated that husbands' smoking raises wives' risk for lung cancer by 30%. The 95% confidence range of the odds ratio in the present study is 0.62 to 1.40 and includes

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1.30 within but a clearcut conclusion could not be drawn from such an uncertain risk factor. The present study also indicated that the effect of smoking by other members of the household, rather than by husbands, tends to be more significant. Shimizu, et al.[13] reported that smoking by fathers-in-law who lived in the same households has a more significant effect than that by husbands.

The analysis in the present study failed to show an increase in the risk of lung cancer in relation to the use of heating equipment. For the use of various heating devices, Leung[17] reported that the use of petroleum stoves raised the risk of lung cancer among women in Hong Kong. In Japan, however, Shimizu[18] conducted a case-controlled study in Nagoya in which no increase in the risk of lung cancer was recognized in association with the use of petroleum stoves.

The most serious problem inherent in the methodology of the present study is a large number of cancer patients (especially those with breast cancer) included in the control. Both the cases and control were nonsmokers and there have been no reports on the relationship between the exposure factor--the subject of the present analysis--and cancer involving other organs. Therefore inclusion of a large number of cancer patients is not considered to present a serious problem. However dominance by a single clinical entity (breast cancer in this instance) is not desirable in view of the nature of the control.

The authors plan further studies using a larger number of patients and an improved analysis of the control.

The authors express their gratitude to Dr. Hanai (Osaka Adult Disease Center) who prepared the original form of the questionnaire for the present survey under the guidance of Dr. Muir (IARC).

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Table 1. Odds Ratio of Passive Smoking in Adulthood (before Hospitalization)

	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
Smoking by Husband		
no	56/229	1.00
yes	64/200	0.94(0.62-1.40)
Smoking by Other Members		
no	77/384	1.00
yes	43/135	1/45(0.94-2.23)

* Adjusted by age at hospital admission.

Table 2. Odds Ratio of Passive Smoking during Childhood

	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
Smoking by Father		
no	47/144	1.00
yes	73/375	0.60(0.40-0.91)
Smoking by Mother		
no	102/473	1.00
yes	18/46	1.71(0.95-3.10)
Smoking by Other Members		
no	95/416	1.00
yes	25/103	1.13(0.69-1.87)

* Adjusted by age at hospital admission.

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Table 3. Odds Ratio When Heating Equipment Which May Be The Cause of Indoor Air Pollution Is Used--Observation in Relation to the Age When the Equipment Was Used

Use of Equipment	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
At Age 15		
not used	37/150	1.00
used	83/369	0.94(0.60-1.45)
At Age 30		
not used	45/212	1.00
used	75/307	1.09(0.72-1.65)
At Present		
not used	65/289	1.00
used	55/230	1.07(0.71-1.60)

* Adjusted by age at admission.

Table 4. Odds Ratio When Foot Warmers Were Used During Sleep--Observation at Each Age Level

Use of the Equipment	Lung Cancer/control	Odds Ratio* (95% Confidence Level)
At Age 15		
not used	76/327	1.00
used	44/192	0.97(0.64-1.47)
At Age 30		
not used	95/429	1.00
used	25/90	0.89(0.53-1.51)
At Present		
not used	119/514	1.00
used	1/5	0.67(0.09-4.99)

* Adjusted by age at hospital admission.

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Table 5. Odds Ratio When Straw and Wood Are Used for Cooking Fuel

Use of the Fuel	Lung Cancer/Control	Odds Ratio* (95% Confidence Level)
At Age 15		
not used	46/252	1.00
used	74/267	1.33(0.87-2.02)
At Age 30		
not used	94/469	1.00
used	26/ 50	1.90(1.09-3.30)
At Present		
not used	123/519	-
used	0/0	-

* Adjusted by age at hospital admission.

Table 6. Age-Adjusted Odds Ratios for Maternal and Paternal Smoking during Childhood; and the Use of Straw and Wood as a Cooking Fuel at Age 30, Calculated by Logistic Regression Analysis

Factors	Odds Ratios (95% Confidence Level)
Maternal Smoking During Childhood	1.82(0.98 - 3.37)
Paternal Smoking During Childhood	0.70(0.43 - 1.16)
Use of Straw and Wood as Cooking Fuel at Age 30	1.78(1.02 - 3.10)

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References

1) Compiled by the Statistical Information Section, Secretariat of Minister of Health and Welfare: 1987 Statistics on Population Dynamics, Association of Health Statistics, 1989.

2) Tominaga, H., Hirose, K., & T. Kuroiwa: Prospect of cancer mortality in Japan. Gan to Kagakuryoho, 16:101-111, 1989.

3) Public Information Section, Secretariat of the Prime Minister's Office: Survey on public attitude toward health and smoking problem, Sorifu, 1989.

4) Sobue, T., et al.: Relationship between cigarette smoking and histologic type of lung cancer, with special reference to sex difference. Jpn. J. Clin. Oncol., 18: 3-13, 1988.

5) Sobue, T., Suzuki, R., Hattori, S., et al.: Lung cancer data bank, Publication by the Organization to Eliminate Lung Cancer from Osaka, 13: 14-17, 1985.

6) SAS Institute, Inc.: SAS User's Guide: Statistics, Version 5 Edition, Gary, NC, 1985.

7) SAS Institute, Inc.: SUGI Supplemental Library User's Guide Version 5 Edition, Gary, NC, 1986.

8) Koo, L.C., et al.: Do cooking fuels pose a risk for lung cancer?: A case-controlled study of women in Hong Kong. Ecol.-Dis., 2: 255-265, 1983.

9) Gao, Y.T., et al.: Lung cancer among Chinese women, Int. J. Cancer, 40: 604-609, 1987.

10) MacLennan, R., et al.: Risk factors for lung cancer in Singapore Chinese, A Population with high female incidence rates. Int. J. Cancer, 20: 854-860, 1977.

11) Tager, I. B., et al.: Longitudinal study of the fffects of maternal smoking on pulmonary functions in children. N. Engl. J. Med., 309: 699-703, 1983.

12) Wu. A., et al.: Smoking and other risk factors for lung cancer in women. JNCI, 74: 747-751,, 1985.

13) Shimizu, H., Morishita, M., Mizuno, K., et al.: Case-controlled study of lung cancer in women. Haigan, 27: 582, 1987.

14) Hirayama, T.: Nonsmoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Brit. Med. J.,

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282: 183-185, 1981.

15) Akiba, S., et al.: Passive smoking and lung cancer among Japanese women. Cancer Res., 46: 4804-4807, 1986.

16) Blot, W. J., et al.: Passive smoking and lung cancer. JNCI, 77: 993-1000, 1986.

17) Leung, J. S. M.: Cigarette smoking, the kerosene stove and lung cancer in Hong Kong. Brit. J. Dis. Chest. 71: 273-276, 1977.

18) Shimizu, H.: Case-controlled study of lung cancer classified according to histological types, Haigan, 23: 127-137, 1983.

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LUNG CANCER AMONG CHINESE WOMEN

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A case-control study involving interviews with 672 female lung cancer patients and 735 population-based controls was conducted to investigate the high rates of lung cancer, notably adenocarcinoma, among women in Shanghai. Cigarette smoking was a strong risk factor, but accounted for only about one-fourth of all newly diagnosed cases of lung cancer. Most patients, particularly with adenocarcinoma, were life-long non-smokers. The risks of lung cancer were higher among women reporting tuberculosis and other pre-existing lung diseases. Hormonal factors were suggested by an increased risk associated with late menopause and by a gradient in the risk of adenocarcinoma with decreasing menstrual cycle length, with a 3-fold excess among women who had shorter cycles. Perhaps most intriguing were associations found between lung cancer and measures of exposure to cooking oil vapors. Risks increased with the numbers of meals cooked by either stir frying, deep frying or boiling; with the frequency of smokiness during cooking; and with the frequency of eye irritation during cooking. Use of rapeseed oil, whose volatiles following high-temperature cooking may be mutagenic, was also reported more often by the cancer patients. The findings thus confirm that factors other than smoking are responsible for the high risk of lung cancer among Chinese women and provide clues for further research, including the assessment of cooking practices.

The age-adjusted annual lung cancer incidence rate among females in Shanghai during the 1970's and 1980's has been about 20 per 100,000 population, one of the highest rates in China and in the world (National Cancer Control Office, 1980; Gao, 1982; Waterhouse *et al.*, 1982; Shanghai Cancer Registry, 1983). Elevated lung cancer death rates have also been observed among Chinese women in other parts of the world, including Hong Kong (Kung *et al.*, 1984; Koo *et al.*, 1985), Singapore (MacLennan *et al.*, 1977) and the United States (Fraumeni and Mason, 1974; Hinds *et al.*, 1981; Green and Brophy, 1982). The high rates of this cancer are surprising since few Chinese women smoke cigarettes (Deng and Gao, 1985). Furthermore, in Shanghai (Zheng and Gao, 1986) and elsewhere, hospital records have indicated that most of the lung tumors are adenocarcinomas, a type of lung cancer less strongly related to smoking (Lubin and Blot, 1984). To explore reasons for the high rates of lung cancer among women in Shanghai, the Shanghai Cancer Institute, in collaboration with the US National Cancer Institute, carried out a population-based case-control investigation. Herein we report the results of this study, quantifying the role of smoking and evaluating a variety of suspected risk factors.

MATERIAL AND METHODS

All newly diagnosed cases of primary lung cancer (9th Revision ICD 162) during the 2-year period February 1984–February 1986 among female residents of urban Shanghai aged 35–69 years were identified by a rapid reporting system for lung cancer established for this study. The system was built upon the existing Shanghai Cancer Registry, the oldest in China (Gao, 1982). Trained staff contacted medical facilities in Shanghai to ascertain new cases, so that interviews could be rapidly scheduled (typically within 2 weeks of diagnosis). The staff reviewed relevant medical records, abstracting data on the basis of diagnosis, histologic type, and the site of the tumor within the lung. Two senior pathologists and 4 senior clinicians were appointed to review the diagnostic information from all cases collected in the study, including X-ray films, cytologic and histologic slides.

Female controls were randomly selected within 5-year age strata from the general population of the Shanghai urban area. The number and age distribution of the controls were determined in advance from the number and age distribution of lung cancer cases reported to the Shanghai Cancer Registry during the period 1980–81. The selection procedure involved randomly choosing a neighborhood committee from among the approximately 1,300 committees in urban Shanghai, then randomly choosing a household group within the committee and ascertaining from existing rosters the names of all females in the appropriate age range. Among these persons, 2 were randomly selected. If the first was absent during the period of study or could not be interviewed, the second was accepted as a control. Tables of random numbers were used in the random sampling.

The cases and controls were interviewed by trained interviewers. A structured questionnaire was used to obtain information on demographic characteristics, exposure to tobacco, dietary and cooking practices, medical conditions, family history of lung cancer, menstrual and reproductive factors, job history and other variables. All completed questionnaires and medical abstracts were checked by a field supervisor, and the information was then abstracted on coding sheets for key-punching and computerization in the United States.

Statistical analyses of the collected data were based on multivariate techniques for case-control data (Breslow and Day, 1980). Logistic regression analyses were used to estimate summary relative risks (RR) of lung cancer associated with various factors, after adjusting for age (<55, 55–59, 60–64, 65–69), smoking (non-smoker; smoked less than 20 years or less than 10 cigarettes/day; smoked 20 or more years and 10–19 cigarettes/day; smoked 20 or more years and 20 or more cigarettes/day), education (no formal education, primary school, secondary school and higher) and other variables, and to evaluate statistical significance. Population attributable risk (PAR) estimates for smoking, adjusted for age, were also derived (Whittemore, 1983).

RESULTS

A total of 765 lung cancer patients were identified during the 2-year period and interviews conducted with 672 (88%). We excluded the 93 patients who died, including 38 ascertained by death certificate only. There were no patients who refused interview. Forty-three percent of the cases were diagnosed by tissue biopsy, 38% by cytology, and 19% by repeated

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TABLE I - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH NUMBER OF CIGARETTES SMOKED PER DAY AND DURATION OF SMOKING

Number of cigarettes smoked per day	Duration of smoking							
	< 30 Years				> 30 Years			
	Cases	Controls	RR[1]	95% CI	Cases	Controls	RR	95% CI
< 10	36	45	1.4	0.9–2.2	34	29	2.4	1.4–4.1
10–19	19	11	2.6	1.2–5.7	56	33	3.2	2.0–5.1
20+	13	2	8.9	2.0–40.2	78	10	14.1	7.1–28.0

[1]Adjusted for age and education. Non-smokers are used as the reference group

TABLE II - RELATIVE RISKS OF LUNG CANCER AMONG NON-SMOKING WOMEN ASSOCIATED WITH YEARS LIVED WITH A SMOKING HUSBAND

Years lived with smoking husband	Cases	Controls	RR[1]	95% CI
< 20	57	99	1.0	—
20–29	63	93	1.1	0.7–1.8
30–39	78	107	1.3	0.8–2.1
≥ 40	48	76	1.7	1.0–2.9

[1]Adjusted for age and education

X-ray films. Among the 542 interviewed cases pathologically or cytologically diagnosed, adenocarcinoma was the predominant cell type accounting for 61% of all cases, 22% were squamous carcinomas, 6% were oat-cell (or small-cell undifferentiated) cancers, and 11% were mixtures and other cell types.

A total of 735 controls were interviewed. Among these 71 (9.7%) were "second" controls, chosen mainly because the first selected control had moved from the Shanghai urban area or was found to be outside the eligible age range. The distributions by age, education and marital status were generally similar between cases and controls. More controls than cases (32% *vs.* 20%), however, were in the oldest age group of 65–69 years, but all subsequent analyses were age-adjusted.

Cigarette smoking

Cigarette smoking was associated with a significantly increased risk of lung cancer, even though only 35% of the lung cancer patients (compared to 18% of the controls) had ever smoked. There was a 3.3-fold excess risk (95% CI = 2.5–4.2) of lung cancer among smokers, but risks were higher for squamous-cell carcinoma (RR = 7.2, 95% CI = 4.6–11.1) and oat-cell cancer (RR = 7.2, 95% CI = 3.6–17.0) than for adenocarcinoma (RR = 1.5, 95% CI = 1.0–2.1). The RR for all lung cancers combined tended to rise with increasing numbers of cigarettes smoked per day and with increasing duration of smoking (Table I). The excess reached 14-fold for females who smoked 20 or more cigarettes per day for more than 30 years. Similar trends existed for adenocarcinoma and for squamous/oat-cell cancers, but the magnitude of the increase was considerably greater for the latter (not shown).

We calculated population-attributable risk (PAR) estimates for smoking in each age group. The PAR rose with age, from 8% to 27% to 28% to 40% at ages < 55, 55–59, 60–64, and 65–69, respectively, primarily because the prevalence of smoking rose with age. In total, we estimated that 24% of all female lung cancers in Shanghai were due to smoking.

Passive smoking

No significant increase in risk was observed for overall exposure to environmental tobacco smoke during childhood (RR = 1.1, 95% CI = 0.7–1.7) or adult life (RR = 0.9, 95% CI = 0.6–1.4). For these calculations, exposure was said to occur if the subject had ever lived with a smoker. When exposure was defined in terms of husband's smoking, however, lung cancer risks among non-smoking women tended to increase with the number of years a woman lived with a husband who smoked, the RR reaching 1.7 among those with 40 or more compared to less than 20 years' exposure (Table II). The risk in this heavily exposed group was even higher (RR = 2.9, 95% CI = 1.0–8.9) for squamous- and oat-cell carcinoma.

Previous lung diseases

Since lung cancer in its early stages may be confused with other lung diseases, we excluded non-malignant lung diseases occurring within the 3 years preceding interview in evaluating the effect of prior lung disease upon lung cancer risk. Table III shows that previous tuberculosis, pneumonia and emphysema were significantly associated with lung cancer risk even after adjusting for smoking. Although some individuals reported having 2 or more of these diseases, the excesses for each persisted when those with multiple conditions were excluded. Further analysis (not shown) indicated that the effect of tuberculosis was not related to the use of isoniazid or streptomycin. While tuberculosis and pneumonia were related to both squamous/oat-cell carcinoma and adenocarcinoma of the lung, emphysema and chronic bronchitis were associated only with the squamous- and oat-cell types.

Cooking practices

Soybean and rapeseed oils were the oils used most often for cooking in Shanghai, with over 95% of women reporting the use of both products. Rapeseed oil, however, was reported as the most often used cooking oil by 52% of the cases compared to 45% of the controls. The overall increase in risk associated with rapeseed compared to soybean as the most often used oil was 1.4 (95% CI = 1.1–1.8). Table IV shows that the excess lung cancer risk associated with use of rapeseed oil existed at each level of reported frequency of eye irritation when cooking, a subjective variable representing severity of exposure to cooking vapors. The calculations for this Table excluded the few women who never cooked, and employed as the reference group women who most often used soybean oil but never or rarely reported eye irritation. Table IV also shows that risks of lung cancer were independently related to eye irritation, with the highest risks (RR = 2.8, 95% CI = 1.8–4.3) among those using rapeseed oil and frequently reporting irritation. The patterns were similar for squamous/oat-cell cancer and adenocarcinoma. We also observed, after adjusting for eye irritation, a 60% higher risk for lung cancer among women who reported considerable or somewhat smoky conditions in their homes when cooking, another rough measure of exposure to cooking vapors and to house ventilation (Table V). In addition, the risk ratios increased with the number of different dishes per week prepared by stir frying, deep frying, or boiling (Table VI). In contrast, no significant case/control differences were associated with the type of fuel used for cooking. The RR and 95% CI associated with coal, gas and wood as the usual fuels were 0.9 (0.7–1.3), 1.1 (0.7–1.5), and 1.0 (0.6–1.8) respectively. There was no trend in risk with increasing years of use of coal, the most common cooking fuel in Shang-

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TABLE III - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH PREVIOUS LUNG DISEASES

Past lung diseases	Controls	All cases	RR[1]	95% CI	Squamous/oat-cell	RR[1]	95% CI	Adeno-carcinoma	RR[1]	95%
None	554	418	1.0	—	80	1.0	—	229	1.0	—
Tuberculosis	61	80	1.7	1.1-2.4	20	2.0	1.1-3.7	42	1.6	1.0-2.5
Pneumonia	35	65	1.9	1.2-3.0	16	1.8	0.9-3.8	26	1.5	0.9-2.7
Emphysema	18	37	2.0	1.0-3.7	19	4.5	2.0-10.3	6	0.7	0.3-2.0
Chronic bronchitis without emphysema	86	112	1.2	0.8-1.7	35	1.4	0.8-2.5	33	0.8	0.5-1.3
Others	30	30	1.3	0.7-2.2	8	1.7	0.7-4.2	13	1.0	0.5-2.0

[1]All risks adjusted for age, education and smoking and relative to women with no reported prior lung disease. Persons with more than one past lung disease are included in each lung disease category.

TABLE IV - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH COOKING OIL USED MOST OFTEN AND FREQUENCY OF EYE IRRITATION WHEN COOKING

Eye irritation when cooking	Oil used most often	Cases	Controls	RR[1]	95% CI
Never or rarely	Soybean	140	214	1.0	—
	Rapeseed	145	193	1.2	0.9-1.7
Sometimes	Soybean	70	72	1.5	1.0-2.3
	Rapeseed	87	63	2.0	1.3-3.0
Frequently	Soybean	59	56	1.4	0.9-2.3
	Rapeseed	90	50	2.8	1.8-4.3
Total	Soybean	269	342	1.0	—
	Rapeseed	322	306	1.4	1.1-1.8

[1]Adjusted for age, education and smoking.

TABLE V - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH FREQUENCY OF EYE IRRITATION AND HOUSE SMOKINESS WHEN COOKING

Eye irritation	House smokiness	Cases	Controls	RR[1]	95% CI
Never/rarely	None/slight	244	380	1.0	—
	Somewhat/considerable	55	55	1.6	1.0-2.5
Sometimes/frequently	None/slight	212	200	1.6	1.2-2.1
	Somewhat/considerable	109	60	2.6	1.8-3.7

[1]Adjusted for age, education and smoking.

TABLE VI - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH NUMBER OF DIFFERENT DISHES PER WEEK PREPARED BY DIFFERENT METHODS OF COOKING

Number of dishes per week	Cases	Controls	RR[1]	95% CI
Stir frying				
≤20	336	408	1.0	—
20-24	198	211	1.2	0.9-1.5
25-29	48	47	1.2	0.8-1.9
≥30	34	15	2.6	1.3-5.0
Deep frying				
0	502	594	1.0	—
1	85	68	1.5	1.0-2.1
2	21	15	1.6	0.8-3.2
≥3	8	4	1.9	0.5-6.8
Boiling				
≤3	96	124	1.0	—
4-7	390	483	1.0	0.7-1.3
8-11	63	40	1.8	1.1-3.0
≥12	67	33	2.2	1.3-3.7

[1]Adjusted for age, education and smoking.

TABLE VII - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH DIETARY INTAKE OF VITAMIN A

Vitamin exposure variable	Quartile level of consumption			
	I (High)	II	III	IV
Vitamin A index	1.0	0.6 (0.5-0.9)	0.8 (0.6-1.1)	0.5 (0.4-0.7)
Retinol-rich foods	1.0	0.9 (0.7-1.3)	1.0 (0.7-1.3)	0.9 (0.7-1.2)
Carotene-rich foods	1.0	0.6 (0.5-0.8)	0.5 (0.4-0.7)	0.5 (0.3-0.6)

[1]Risk relative to highest quartile of consumption and adjusted for age, education and smoking. 95% CI in parentheses.

hai. Exposures to coal or other fuel fumes were generally associated only with cooking, since nearly all homes in Shanghai were unheated.

Diet

The women were asked about their usual frequency of consumption during adulthood of 32 commonly eaten foods, including the major contributors of vitamin A. Using Chinese food composition tables to estimate the retinol and carotene content of each food and applying these estimates to its frequency of intake, an index of vitamin A consumption in retinol-equivalent units was constructed. The risks for lung cancer tended to be lower among those with low values of this index (Table VII). This association was accounted for mainly by a lower risk among those with a reduced consumption of carotene-rich foods (the dominant source being dark green vegetables). No effect on risk was found for consumption of the retinol-rich foods (mainly fish, eggs and liver). The patterns were generally similar for squamous/oat-cell cancer and adenocarcinoma, and for smokers and non-smokers.

Menstrual and reproductive factors

The risks of lung cancer were higher among women with shorter menstrual cycle lengths (Table VIII). The association was primarily seen for adenocarcinoma, which showed a strong dose-response relationship. Among women aged 55 years and over with a natural menopause, the risk of adenocarcinoma tended to increase with the total number of menstrual cycles over their lifetime. Some increased risk of adenocarcinoma was seen when natural menopause occurred at age 50 or later (RR = 1.3, 95% CI = 0.9-1.7, after adjusting for menstrual cycle length). No associations were seen with age at menarche, age at first pregnancy, or parity.

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TABLE VIII - RELATIVE RISKS OF LUNG CANCER ASSOCIATED WITH LENGTH OF MENSTRUAL CYCLE

Length of menstrual cycle (days)	All cases	Controls	RR[1]	95% CI	Squamous oat-cell	RR[1]	95% CI	Adeno-carcinoma	RR	95% CI
>33	43	60	1.0	—	12	1.0	—	18	1.0	—
30-33	272	327	1.6	1.0-2.6	62	0.9	0.4-2.0	124	1.9	1.0-3.5
26-29	241	268	1.6	1.0-2.7	51	0.8	0.4-1.9	127	2.1	1.1-3.9
<26	98	78	2.2	1.3-3.7	23	1.6	0.7-3.9	54	2.9	1.5-5.7

[1]Adjusted for age, education, smoking and regularity of menstruation

TABLE IX - RELATIVE RISKS OF LUNG CANCER FOR WOMEN EVER EMPLOYED IN MAJOR OCCUPATIONAL GROUPS

	Occupation category[1]	Cases	Controls	RR[2]	95% CI
I-II	Professionals and technicians; leaders of state organizations, party and mass organizations and enterprise units	113	116	1.0	0.7-1.4
III-IV	Office and related personnel; sales workers	75	96	0.7	0.5-1.0
V	Service workers	159	160	1.0	0.8-1.4
VI	Agricultural, forestry, animal husbandry and fishery workers	24	21	1.1	0.6-2.1
VII-IX	Production, transportation and other related workers	436	471	1.1	0.9-1.4
0	Never worked	61	75	1.1	0.7-1.6

[1]Women employed in more than one occupational category are included in each category in which they worked. The coding scheme was based on the system used in the 1982 Population Census of the People's Republic of China (Population Census Office, 1985). [2]Adjusted for age, education and smoking.

Occupation

Most women reported working outside the home, but case/control differences according to major occupational categories were small (Table IX). No major occupations were associated with increased risk of lung cancer. A decreased risk, however, was observed for women ever employed in the cotton textile industry, the largest employer of women in Shanghai. There was a slight increase in the relative risk of lung cancer among women ever employed as cooks (RR = 1.2, 95% CI = 0.6-2.1), but few worked longer than 20 years.

Family history

The cancer patients reported about the same frequency of lung cancer in their mothers (1.0%) and fathers (1.7%) as the controls (1.0% and 1.5%, respectively). The RR, adjusted for age, education and smoking, associated with having a parent with lung cancer was 1.1 (95% CI = 0.6-2.3). More sibs were reported to have lung cancer, but the numbers affected were small (6 cases, 3 controls; RR = 3.0, 95% CI = 0.7-12.5). Only one child, of a control, had lung cancer.

DISCUSSION

The high incidence of lung cancer among women in Shanghai, together with the low prevalence of smoking in the general population, led us to consider a number of possible etiologic factors. While cigarette smoking was an important cause of lung cancer, showing a clear dose-response trend, the majority of lung tumors, particularly adenocarcinomas, occurred among non-smokers.

Environmental tobacco smoke may account for some, but probably few, of the cancers among non-smokers, since there was little or no association with ever having lived with a smoker. Among non-smoking women married to smokers, however, there was an upward trend in risk associated with increasing years of exposure. This latter finding is consistent with reports in other parts of the world. When data from nearly a dozen studies evaluating passive smoking were combined (Blot and Fraumeni, 1986), an overall 30% excess of lung cancer (RR = 1.3, 95% CI = 1.1-1.5) was found among non-smoking women married to smokers, with the RR reaching 1.7 among those most heavily exposed.

Although the causal significance of the relation of prior lung disease to lung cancer remains to be clarified, the high prevalence of previous pulmonary infections may have contributed in part to the high incidence of lung cancer among Shanghai women. Earlier in this century, non-malignant lung disease was one of the leading causes of death in China (Kan, 1981). With the advent of antibiotics and improved living conditions, the incidence and mortality of chronic lung diseases, particularly tuberculosis, declined. Nevertheless, a substantial portion (38%) of the women with lung cancer in this study reported prior lung disease, including 12% who were long-term survivors of tuberculosis, whereas significantly lower percentages of controls reported these diseases. To some extent it is possible that recall or ascertainment bias may contribute to the associations observed with prior lung diseases. The elevated risk of lung cancer following tuberculosis, however, is consistent with recent studies in other countries, and is not explained by cigarette smoking or treatment with isoniazid, a pulmonary carcinogen in laboratory animals (Howe *et al.*, 1979; Hinds *et al.*, 1982; Bakris *et al.*, 1983).

Emphysema was also significantly related to lung cancer, after adjustment for smoking habits, with the excess limited to squamous- and oat-cell carcinomas. This finding adds to the evidence that chronic obstructive pulmonary disease enhances the risk of lung cancer (Skillrud *et al.*, 1986), even when controlling for smoking practices. Also noteworthy is the elevated risk associated with prior pneumonia, especially since an association with lung adenocarcinoma has previously been reported among women in Los Angeles (Wu *et al.*, 1985). While pneumonia typically occurred during adulthood in our study, the finding in Los Angeles primarily concerned childhood infection.

Little evidence was found to implicate the type of fuels used for cooking in lung cancer risk, consistent with findings from

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Hong Kong (Koo *et al.*, 1983). The risks of lung cancer among Shanghai women increased, however, with various measures of exposure to cooking oil vapors. These included the number of different dishes prepared per week by either stir frying, deep frying, or boiling; the frequency of eye irritation when cooking; and the smokiness of the house when cooking. In Chinese wok cooking, regardless of the method used, oil is usually poured into a wok and heated to high temperatures before meat or vegetables are added. Even boiling may entail some exposure to cooking oil vapors, since oil is often added to the water before heating. Consequently, the living quarters may become smoky during cooking, with opportunity for exposure to inhalable cooking oil vapors.

The plausibility of the hypothesis that lung cancer may be related to cooking oil vapors, particularly from rapeseed oils used in Shanghai, is enhanced by recent experimental investigations. In one study the mutagenicity of products from cooking oil was assayed by the Ames test (Qu *et al.*, 1986). The extracts of condensed volatiles of rapeseed oil, refined rapeseed oil, and soybean oil heated at about 270°C were all positive in tester strain TA98 activated with S9. The mutagenicity of the extract from rapeseed oil volatiles was stronger than that from soybean oil volatiles. There was no evidence of mutagenicity in the oils themselves, either heated or unheated. In another study, the extracts of condensed volatiles of rapeseed oil enhanced the yield of micronuclei in polychromatic erythrocytes of the bone marrow of mice, with a clear dose-response relationship, reflecting damage of chromosomes and cell genotoxicity by rapeseed oil volatiles (Chen, 1987). Although these tests often correlate with carcinogenic potential, no bioassay studies have yet been carried out, to our knowledge. If the effect of rapeseed oil smoke on lung cancer incidence is real, the problem is of great importance to populations of eastern central China and other areas of the world where the oil is often used for cooking. Chinese rapeseed oil, which is pressed from seeds of *Brassica campestris*, contains about 50% erucic acid (Chinese Academy of Medical Sciences, 1981), in contrast to rapeseed oil with <2% erucic acid (Canbra oil), which was recently approved for sale in the United States (Federal Register, 1985).

Several studies have shown that the risk of lung cancer is elevated by a low intake of foods containing vitamin A, particularly as its precursor beta-carotene (Colditz *et al.*, 1987). Although reported mainly in Western countries, this association has also been noted among Chinese women in Singapore (MacLennan *et al.*, 1977). However, we found no evidence of a protective effect among women in Shanghai, where intake of fresh, carotene-rich, dark green vegetables is high by world standards. In fact, a positive association was observed between carotene intake and lung cancer risk in females (in contrast to no association in males). We have no ready explanation for this unusual finding in females, which was observed also in a case-control study of lung cancer in Hawaii (Hinds *et al.*, 1984). However, the protective effect of carotene-rich foods was mainly confined to current smokers in one large-scale study (Ziegler *et al.*, 1986), and thus the effect may be less evident in Shanghai where few women smoke.

A clue to hormonal factors was suggested by an association between menstrual cycle length and lung adenocarcinoma. A 3-fold difference in adenocarcinoma risk was found among Shanghai women reporting short (<26 days) compared to long (>33 days) menstrual cycles, with only a weak trend for squamous- and oat-cell cancers. A relation of short menstrual cycles to breast cancer risk has been suggested in data from Sweden (Olsson *et al.*, 1983) and, to a lesser extent, the United States (Sherman *et al.*, 1982). Some increases in lung adenocarcinoma risk were also associated with late menopause and with a high estimated total number of menstrual cycles among women aged 55 and over having a natural menopause. A role of hormonal factors is also suggested by the observation that among non-smokers adenocarcinoma affects proportionately more females than males (Lubin and Blot, 1984), and by the findings of estrogen and progesterone receptors in some lung adenocarcinomas of women (Chaudhuri *et al.*, 1982). We discovered no relation to oral contraceptives or replacement estrogen therapy, but use of these compounds among women in the study group was rare in Shanghai. It seems unlikely that the menstrual patterns of Chinese women contribute greatly to their high lung cancer risk, but the internal consistency of the trends suggests that future studies of lung cancer in China and elsewhere should examine endocrine hypotheses in more detail.

This large population-based case-control study of lung cancer in urban Shanghai has confirmed that cigarette smoking is a strong risk factor among Chinese women, but only accounts for about one-fourth of all newly diagnosed cases. Causes of the remainder are unclear, but occupational factors did not appear to be important, nor did familial tendency to lung cancer. Our data suggest, however, that prior lung diseases, hormonal factors, and cooking practices may be involved. Most provocative are the associations with cooking oil volatiles, and further investigations are needed to evaluate their contribution to the high lung cancer rates among Chinese women in various parts of the world.

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REFERENCES

Bakris, G., Mulopulos, G.P., Korchik, R., Ezdinli, E., Ro, J., and Yoon, B., Pulmonary scar carcinoma. *Cancer*, **52**, 493–497 (1983).

Blot, W.J., and Fraumeni, J.F., Jr., Passive smoking and lung cancer. *J. nat. Cancer Inst.*, **77**, 993–1000 (1986).

Breslow, N.E., and Day, N.E., *Statistical methods in cancer research. The analysis of case-control studies. IARC Scientific Publicanon*, **32**, pp. 192–246. IARC, Lyon (1980).

Chaudhuri, P.K., Thomas, P.A., Walker, M.J., Briele, H.A., Gupta, T.D., and Beattie, C.W., Steroid receptors in human lung cancer cytosols. *Cancer Lett.*, **16**, 327–332 (1982).

Chen, T.D., Micronucleus test of condensed volatiles of rapeseed oil. *Tumor*, 1987 (in press).

Chinese Academy of Medical Sciences. *Food composition tables*. People's Health Publishing Co., Beijing (1981).

Colditz, G.A., Stampfer, M.J., and Willet, W.C., Diet and lung cancer: a review of the epidemiologic evidence in humans. *Arch. intern. Med.*, **147**, 157–160 (1987).

Deng, J., and Gao, Y.T., Prevalence of smoking among 110,000 adult residents in Shanghai urban area. *Chinese J. prev. Med.*, **19**, 271–274 (1985).

Federal Register, Vol. **50**, No. **18**, US Government Printing Office, Washington, DC (1985).

Fraumeni, J.F., and Mason, T.J., Cancer mortality among Chinese Americans, 1950–1969. *J. nat. Cancer Inst.*, **52**, 659–665 (1974).

Gao, Y.T., Cancer incidence in Shanghai during 1973–77. *Nat. Cancer Inst. Monogr.*, **62**, 43–46 (1982).

Green, J.P., and Brophy, P., Carcinoma of the lung in non-smoking Chinese women. *West. J. Med.*, **136**, 291–294 (1982).

2023381779

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HINDS, M.W., COHEN, H.I., and KOLONEL, L.N., Tuberculosis and lung cancer risk in non-smoking women. *Amer. Rev. resp. Dis.*, **125**, 776–778 (1982).

HINDS, M.W., KOLONEL, L.N., HANKIN, J.H., and LEE, J., Dietary vitamin A, carotene, vitamin C and risk of lung cancer in Hawaii. *Amer. J. Epidemiol.*, **119**, 227–237 (1984).

HINDS, M.W., STEMMERMAN, G.N., YANG, H.Y., KOLONEL, L.N., and LEE, J., Differences in lung cancer risk from smoking among Japanese, Chinese and Hawaiian women in Hawaii. *Int. J. Cancer*, **27**, 297–302 (1981).

HOBBY, G., LINDSAY, J., COPPOCK, E., and MILLER, A.B., Isoniazid exposure in relation to cancer incidence and mortality in a cohort of tuberculosis patients. *Int. J. Epidemiol.*, **8**, 305–312 (1979).

KAN, G., Tuberculosis and its control in Beijing. *Chin. med. J.*, **94**, 685–690 (1981).

KIANG, L.C., HO, J.H., and LEE, N., An analysis of some risk factors for lung cancer in Hong Kong. *Int. J. Cancer*, **35**, 149–155 (1985).

KIANG, L.C., LEE, N., and HO, J., Do cooking fuels pose a risk for lung cancer? A case-control study of women in Hong Kong. *Ecol. Dis.*, **2**, 255–265 (1983).

KUNG, J., SO, K., and LAM, T., Lung cancer in Hong Kong Chinese: mortality and histologic types 1973–1982. *Brit. J. Cancer*, **50**, 381–388 (1984).

LUBIN, J., and BLOT, W.J., Assessment of lung cancer risk factors by histologic category. *J. nat. Cancer Inst.*, **73**, 383–398 (1984).

MACLENNAN, R., DA COSTA, J., DAY, N.E., LAW, C.H., NG, Y.K., and SHANMUGARATNAM, K., Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. *Int. J. Cancer*, **20**, 854–860 (1977).

NATIONAL CANCER CONTROL OFFICE. *Atlas of Cancer Mortality in the People's Republic of China*. China Map Press, Beijing (1980).

POPULATION CENSUS OFFICE. 10 Percent Sampling Tabulation on the 1982 Population Census of the People's Republic of China. China Statistical Publishing House, Beijing (1985).

OLSSON, H., LANDIN-OLSSON, M., and GULLBERG, B., Retrospective assessment of menstrual cycle length in patients with breast cancer, in patients with benign breast disease, and in women without breast disease. *J. nat. Cancer Inst.*, **70**, 17–21 (1983).

QU, Y.H., XU, G.X., HUANG, F., FANG, J.C., and GAO, Y.T., An Ames test on the by-products of the heating of cooking oils. *Tumor*, **6**, 58–60 (1986).

SHANGHAI CANCER REGISTRY. *Annual Reports on Cancer Incidence and Mortality: Data in Shanghai Urban Area*, Shanghai Cancer Institute, Shanghai (1983).

SHERMAN, B.M., WALLACE, R.B., and BEAN, J.A., Cyclic ovarian function and breast cancer. *Cancer Res. (Suppl.)*, **42**, 3286–3288 (1982).

SKILLRUD, D.M., OFFORD, K.P., and MILLER, R.D., Higher risk of lung cancer in chronic obstructive pulmonary disease: a prospective matched controlled study. *Ann. intern. Med.*, **105**, 503–507 (1986).

WATERHOUSE, J., MUIR, C., SHANMUGARATNAM, K., and POWELL, J., *Cancer incidence in five continents*, Vol. IV, IARC, Lyon (1982).

WHITTEMORE, A.S., Estimating attributable risks from case-control studies. *Amer. J. Epidemiol.*, **117**, 76–85 (1983).

WU, A., HENDERSON, B.E., PIKE, M.C., and YU, M.C., Smoking and other risk factors for lung cancer in women. *J. nat. Cancer Inst.*, **74**, 747–751 (1985).

ZHENG, W., and GAO, Y.T., A hospital-based case-control study on association of squamous cell carcinoma and adenocarcinoma with smoking. *Tumor*, **6**, 17–20 (1986).

ZIEGLER, R.G., MASON, T.J., STEMHAGEN, A., HOOVER, R., SCHOENBERG, J., GRIDLEY, G., VIRGO, P.W., and FRAUMENI, J.F., JR., Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. *Amer. J. Epidemiol.*, **123**, 1080–1093 (1986).

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Dietary Habits and Lung Cancer Risk Among Chinese Females in Hong Kong Who Never Smoked

Linda C. Koo

Abstract

This describes a retrospective study in which 88 lung cancer patients and 137 district-matched controls were interviewed concerning the effects of diet on lung cancer risk among Hong Kong Chinese women who never smoked tobacco. Those in the lowest tertile of consuming fresh fruit or fresh fish had statistically significant adjusted relative risks (RRs) of 2.4 and 2.8, respectively. The protective effects of diet, i.e., higher consumption of leafy green vegetables, carrots, tofu, fresh fruit, and fresh fish, were confined mostly to those with adenocarcinoma or large cell tumors. Only fresh fruit was found to positively, and smoked meats to negatively, affect the risk of squamous or small cell tumors. Foods high in vitamin C, retinol, and calcium seemed to exert larger effects. Subjects from larger households were shown to be more frequent consumers of fresh vegetables, fruit, and fish. Because the lifetime weighted household size could be used as a surrogate index of past dietary quality, when it was combined with current dietary intakes of fresh fruit, the RR increased as either factor decreased in a dose-response manner. The adjusted RR was 5.8 at the lowest level. Further testing of the validity of the lifetime weighted household size as an index of past dietary quality is needed.

(Nutr Cancer 11, 155–172, 1988)

Introduction

Lung cancer among females in Hong Kong is notable because the world age-adjusted incidence rate of 27.1 per 100,000 for 1982 (1) ranked it among the highest in the world and because 64% of the cases with lung cancer were not found to be attributable to a history of active smoking (2). Although lung cancer has been the major cause of cancer death among both men and women in Hong Kong since the mid-1970s, the world age-adjusted incidence rate for men of 63.6 per 100,000 (1) in 1982 was not unusual for an urban industrialized society, where 95% of the cases (2) were attributed to smoking. Thus, a case-control study of female lung cancer was conducted from 1981 to 1983 to explore possible environmental

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factors contributing to the high rates of this cancer among Chinese females in Hong Kong. These factors would probably be of recent introduction because the mortality rate for female lung cancer increased threefold from 1961 to 1980 (3).

In recent years, exposure to environmental tobacco smoke has been linked in some epidemiological studies to an increased risk for lung cancer among nonsmoking females (4–10). This possibility was studied in detail in our Hong Kong studies (3,11), and although early reports showed no statistically significant increased risks from such exposures, a more recent analysis of the data (12) suggested that such a link might exist among women with squamous cell tumors situated in the peripheral areas of the lung. However, less than 25% of females who never smoked but were lung cancer patients had these types of tumor characteristics, and the small numbers of cases for analyses left these findings very tentative.

One of the major criticisms of studies on passive smoking and lung cancer is that the association might really reflect the fact that wives with husbands who smoke(d) have different life-styles and past exposures than those whose husbands never smoked. This possibility was explored in an analysis of life history correlates of passive smoking among 136 Hong Kong Chinese wives who never smoked (13). Among the 97 quantifiable variables that were studied, data from dietary habits were among the clearest in showing a statistically significant difference in the dietary intakes of the wives based on their husbands' smoking habits. Wives with husbands who had never smoked more frequently consumed cruciferous vegetables, carrots, beans/legumes, and milk. In comparison, wives with husbands who had ever smoked during their marital life together were more frequent consumers of cured/smoked meats, fish (fresh and preserved), pickled vegetables, and chilies/chili sauces. According to the US National Research Council's 1982 report *Diet, Nutrition, and Cancer* (14) the foods more frequently consumed by the former group were identified as protective of cancer and that of the latter to be associated with higher risk for cancer. As a consequence, the direct role of diet in lung cancer risk among those who never smoked in Hong Kong needed further exploration.

It is well known that the human diet includes a large variety of carcinogens, promoters, and anticarcinogens that may be natural or added to food (15). Some, like *N*-methyl-*N*-formylhydrazine found in certain types of edible mushrooms need only be ingested in small amounts (e.g., 20 μg daily) to produce lung tumors in mice (15). Others, like vitamins A, C, and E, are micronutrients with anticarcinogenic activity; this is probably because they are antioxidants.

Epidemiological studies on diet and lung cancer have been relatively consistent in showing the protective effects of ingesting vegetables (16–18) or food sources of vitamin A (19–26). Most studies found these protective effects to be stronger among smokers (16,18,23,26) or exsmokers (17,19,21,24); no studies did separate analyses on subjects who never smoked, mostly because of inadequate sample sizes. Although some of the studies (16,18–24) made statistical adjustments for smoking (to reduce confounding effects) and found the effects to be statistically independent of smoking, it is still questionable as to whether these data are applicable for subjects who never smoked. This is because having a history of smoking may imply other life-style exposures/habits or irreparable damage/changes to the respiratory tract. Furthermore, because some studies (22,26) did not find these protective effects to be applicable to females, further studies seem warranted.

Subjects and Methods

Definition of Cases and Controls

From an initial retrospective case-control study conducted from 1981 to 1983 that covered 200 female lung cancer patients and 200 female district-matched controls, this analysis only

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includes 88 cases and 137 controls who reported no history of active smoking. Subjects who never smoked were defined as those who had smoked less than 20 cigarettes or pipes in the past. All lung cancer patients were interviewed at the hospital when they were receiving in- or out-patient care, and all controls were interviewed at their homes. The lung tumors were histologically typed according to the World Health Organization's histological classification of lung tumors (27). Further details concerning subject selection, lung cancer histological typing, and interview technique and content have been previously described (3,11-13).

The mean ages of the patients and controls were 57.8 (SD 10.8) and 59.3 years (SD 9.9), respectively. Among all the subjects, 66% were currently married (n = 149), 27% were widows (n = 60), 6% were separated or divorced (n = 13), and 1% had never married (n = 3). None of the women had remarried.

Demographic data collected during the interviews included a detailed listing of the number of household members living together for each residence since birth. A lifetime weighted household size index was calculated by a summation of the number of people residing in each address multipled by the number of years that they lived together at that residence then divided by the age of the subject.

Equation is as follows.

$$\frac{\Sigma \text{ (No. of people in each address} \times \text{years at that address)}}{\text{Age of subject}}$$

It is a Σ, not simple addition.

Dietary Data

The dietary section of the interview inquired about the frequency of consumption of a list of food items or food groups. Cases were asked to report on their usual food habits one year before their diagnosis of cancer or the appearance of symptoms. Controls were asked to recall their current usual habits of eating. In the design of the study for all 200 cases and controls, each control was usually interviewed within six weeks of her matched case's interview to reduce the effects that seasonal availability might have on her recall of food consumption habits.

The Chinese style of eating makes it difficult to assess dietary quality, quantity, and frequency. It is common for one dish to be composed of small slices of meat(s) and various mixtures of fresh and pickled/preserved vegetables. When two or more persons are eating together, the dishes are put at the center of the table and one picks up a chopstick full of food each time. Thus, except for the bowl of rice, which is individually portioned, it is extremely difficult to recall the amounts and items of food one has eaten over the meal.

Realizing these difficulties, data gathering concentrated on eliciting consumption patterns of broad groups or types of food: cruciferous vegetables, fresh leafy green vegetables, beans/legumes, tofu/soy products, fresh fruit, fresh fish, dried/salted fish, smoked/cured meat/poultry, fermented fish/shrimp sauces, fermented beans/sauces, chilies/chili sauces, and pickled vegetables. The other advantage of categorizing the food into similar groups is that the large variety of dishes in Chinese cooking is based on working with these categories. For example, one can substitute sliced beef for sliced pork or one type of vegetable for another in a mixed dish composed of many ingredients. Thus, the substitutions occur in set patterns based on these broad food groups, and this eliminated the problem of asking about the hundreds of ingredients that make up the inventory of food items in the local diet. The subjects were also asked about consumption of carrots, the addition of monosodium glutamate in home cooking, and milk drinking patterns, because these items were of specific interest.

The original interview also covered beverages. Specific questions on the types of tea that

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the subject preferred drinking revealed about seven common types of black (fermented) or green (unfermented) teas. In this analysis, only those subjects who preferred to drink plain boiled water will be compared with those who preferred any type of tea. The question on milk consumption was modified to take into account that the adult population of this age group rarely drink just milk alone. Instead, milk could be added to tea, coffee, cocoa, or malted milk mixtures. Thus, the subjects were asked about the period of time when the equivalent of one cup of fresh milk would be consumed.

All subjects were asked about their alcoholic drinking patterns from a list of Chinese and western alcoholic drinks that included liquor, wines, and Chinese tonic wines (tinctures made of medicinal herbs). Because most Chinese women (70–80%) do not drink alcohol, all the alcoholic drinks were combined and subjects were classified as to whether they drank any type of alcohol one or more times a week (yes/no); this distinguished the regular drinkers from the infrequent social drinkers.

Subjects were asked to classify their frequency of eating each food item into one of the following categories: a) never, b) <1/month, c) 1–3/month, d) 1–4/week, e) 5–7/week, and f) ≥ 2/day. In the analysis of the average number of times these foods would be consumed per month, the conversion was done by giving each of the above categories the following weights, respectively: 0, 1, 2, 11, 26, and 61.

Statistical Analysis

The cases and controls were grouped into tertile levels of consumption (low, medium, and high) for statistical calculations of relative risk (RR). For ease of interpretation, the baseline value of 1.00 for protective items in the diet was set at the high levels of consumption, and the reverse was done for food items with detrimental effects. To conserve space in the tables, the definition of each tertile grouping in terms of the baseline value, the first level, and the second level were coded using the frequency categories given in the paragraph above (a to f), in the following manner: (A) = a+b, c, d+e+f; (B) = a+b+c+d, e, f; (C) = a+b+c, d, e+f; (D) = a, b+c, d+e+f; (E) = f+e+d, c, b+a; (F) = a, b, c+d+e+f; and (G) = f+e+d+c, b, a. In the analysis of nutrient levels, where the values for each food item were converted to the times per month, the definition of the tertile groupings per month were as follows: (H) ≤ 7.6, 7.7–16.25, >16.25; (I) ≤ 7.4, 7.5–18.0, >18.0; (J) ≤ 9.0, 9.1–13.0, >13.0; (K) ≤ 13.3, 13.4–20.8, >20.8; and (L) ≤ 10.2, 10.3–14.7, >14.7.

Relative risk calculations included the crude unadjusted (RR1) or adjusted (RR2) odds ratios (28). The latter were estimated by the use of a conditional logistic regression package, PECAN (29), of N:M matching by strata defined by district ($n = 34$) and housing type (public or private). This type of matched analysis was done to control for the effects of socioeconomic status. We had previously studied the effect of all variables in the data set to see their individual effects on lung cancer risk. From this, the following variables were identified as important possible confounders and the adjusted odds ratios took into account age (<50, 50–69, 70+ years), any formal schooling (yes/no), and the number of live births. Although the effects of alcohol were tested in the design of the model, adjustments for alcohol did not affect the relative risks in an additive or interactive way. Similarly, since 11.4% of the cases and 10.9% of the controls reported previous consumption of vitamins, with an average of 6.4 and 3.6 years of consumption, respectively, adjustments for vitamin consumption did not improve the logistic model.

In recognition of the fact that the original study of all 200 cases and controls was based on 1:1 matching by district and housing type, the 95% confidence intervals for the crude odds ratios were estimated from the N:M matched analysis with the value for each variable considered as its exact value. Similarly, this was done for the Mantel-Haenszel trend test for the unadjusted odds ratios. To conserve space in the tables, only the 95% confidence intervals of RR with P values ≤ 0.10 will be given.

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Results

Table 1 shows that a more frequent consumption of fresh fruit or fresh fish conferred protection against lung cancer. Those at the lowest tertiles of consumption had adjusted RR of 2.4 for fresh fruit or 2.8 for fresh fish, and these results and the trend P values were statistically significant. Consumers of alcohol had adjusted RR of 1.85 (95% CI = 0.93–3.70), and the adjusted trend was of borderline significance ($p = 0.08$).

In Table 2, cases were analyzed by histological type. Those with squamous or small cell cancers, and those with adenocarcinoma or large cell cancers were combined because the former group were more closely associated with active smoking than the latter (2). In general, the protective effects of diet were more apparent among those with adenocarcinoma or large cell lung tumors. Among them, the adjusted RR of those who most infrequently consumed the following were: fresh leafy green vegetables 3.09, carrots 6.69, tofu or soy bean products 3.51, fresh fruit 1.55, and fresh fish 3.61. The finding that fermented seafood sauces like shrimp or fish sauces were protective in higher amounts may have been due to the fact that these condiments are frequently added to cooked vegetable dishes.

By contrast, only the consumption of fresh fruit showed a protective trend among those with squamous or small cell tumors, and less frequent consumption of smoked meat/poultry was of borderline significance.

As a heuristic exercise to understand the effects of foods which have in common certain nutrients that have been cited in the literature as being protective of cancer, the data were analyzed (Table 3) by four nutrient indexes: β-carotene, retinol, calcium, and vitamin C. Because data on quantities of food eaten per meal were not collected, and because the Chinese style of eating mixed vegetables and meat/poultry in one dish would not be conducive to assigning a standardized "portion" as in western foods, individual weights of the nutrient to each food type were not done to avoid giving a false sense of precision. The monthly frequencies of consumption of each food item per person were summed and then divided by the total number of items to obtain the average frequency per month for each subject. A dietary variable, "Good Diet," was developed which combined the monthly consumption frequencies of fruits, vegetables, soy products, soup, milk, and fresh fish. This was the diet recommended by the US National Research Council (14) as being protective of cancer and heart disease.

The analysis of all subjects showed that sources of vitamin C (e.g., fresh vegetables and fruit) seemed to confer the most protection against cancer, with the RR around 2 and the P values for trend 0.01. Also, sources of retinol (e.g., fish and milk) were associated with an RR of 2.1–2.4 at the lowest tertile of consumption.

In all the analyses in Table 3, none of the RR or trends for squamous or small cell tumors were statistically significant at the $p \leq 0.05$ level. By comparison, the oppsosite was true for the adenocarcinoma or large cell tumors. All the trend values for each nutrient index were significant or nearly significant, and the RR values were especially elevated for foods high in vitamin C or retinol.

The combined variable Good Diet had the most consistent dose-response model for all subjects, especially those with adenocarcinoma or large cell tumors. The highly significant RR values had a range of 2.1–2.3 for all subjects, and 3.2–3.6 for those with adenocarcinoma or large cell tumors; the P values for trend ranged from 0.001 to 0.003. Again, protective effects were not seen for squamous or small cell tumors.

During the interviews, a few questions directly or indirectly indicating eating habits or tendencies in the subject's household were found to affect the risk ratios (Table 4). The frequencies of consuming Dim Sum (which is the consumption of small savory and sweet dishes for breakfast or lunch at restaurants) and home-cooked soup (which is a Cantonese specialty served frequently as a tonic) (30) did not indicate any statistically significant results.

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Table 1. Frequency of Food Consumption and Lung Cancer Relative Risks[a]

	Frequency of Consumption[b]									Trend *P* Value	
	Low			Medium			High				
	No. of Cases/ Controls	RR1	RR2	No. of Cases/ Controls	RR1	RR2	No. of Cases/ Controls	RR1	RR2	RR1	RR2
Food items/groups[c]											
Cruciferous vegetables (A)	38/61	1.33	1.04	43/61	1.51	1.14	7/15	1.00	1.00	0.702	0.358
Fresh leafy green vegetables (B)	14/15	1.49	2.06	25/44	0.90	1.00	49/78	1.00	1.00	0.212	0.241
Carrots (A)	22/38	1.64	1.96	60/82	2.07	2.57 (1)	6/17	1.00	1.00	0.453	0.404
Beans/legumes (A)	40/59	0.93	0.66	40/66	0.83	0.63	8/11	1.00	1.00	0.952	0.766
Tofu/soy products (A)	20/25	1.98	1.46	51/70	1.80	1.56	17/42	1.00	1.00	0.332	0.524
Fresh fruit (C)	23/22	2.19 (2)	2.39 (3)	21/23	1.91 (4)	1.93 (5)	44/92	1.00	1.00	0.002	0.002
Fresh fish (B)	42/40	2.24 (6)	2.83 (7)	23/48	1.02	1.10	23/49	1.00	1.00	0.021	0.017
Dried/salted fish (E)	43/69	1.00	1.00	27/34	1.27	1.30	18/34	0.85	0.95	0.814	0.865
Smoked/cured meat/poultry (E)	36/51	1.00	1.00	31/54	0.81	0.82	21/32	0.93	0.92	0.944	0.691
Spices and sauces											
Monosodium glutamate at home (D)	63/88	1.00	1.00	14/21	0.93	1.24	11/27	0.57	0.77	0.622	0.960
Fermented fish/shrimp sauce (G)	25/41	1.00	1.00	46/53	1.42	1.23	17/43	0.65	0.64	0.812	0.623
Fermented beans/sauces (E)	28/47	1.00	1.00	45/49	1.54	1.67	15/41	0.61	0.82	0.499	0.827
Chili, fresh and sauce (G)	52/85	1.00	1.00	16/17	1.54	1.67	19/34	0.91	1.03	0.279	0.200
Pickled vegetables (E)	15/34	1.00	1.00	32/43	1.69	1.50	41/60	1.55	1.60	0.962	0.776
Beverages											
Milk (F) (1 cup)	22/43	0.86	1.08	25/25	1.68	1.81	41/69	1.00	1.00	0.243	0.309
Any type of alcohol (no/yes)	61/108	1.00	1.00	27/29	1.65	1.85 (8)				0.163	0.076
Any type of tea (no/yes)	30/52	1.00	1.00	58/85	1.18	1.59				0.333	0.150

a: RR1, unadjusted odds ratio; RR2, odds ratio adjusted for age, no. of live births, and schooling (+ / -). *P* value of trend by exact values of RR1 and RR2.

b: Gives 95% confidence intervals as follows (nos. in parentheses): (1) 0.89-7.40, (2) 1.22-5.55, (3) 1.09-5.23, (4) 0.97-4.26, (5) 0.88-4.24, (6) 1.26-5.03, (7) 1.33-6.00, (8) 0.93-3.70.

c: For (A)-(G), definition of each level of consumption is given in text.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

However, types of cooking oil did lead to statistically significant results. Those who used peanut oil or rapeseed oil (and not corn oil) had RR values of 2.7–3.2. However, it is questionable whether it is the corn oil itself that is protective. Rather, because of the recent media advertisements proclaiming the health benefits of corn oil for cardiovascular disease and avoiding peanut oil for its aflatoxin levels, those housewives who responded to this change indicated their receptivity to behavioral modification for health reasons. This is because for Chinese cooking, peanut oil produces more flavorful cooking and reaches a higher temperature for the stir-fry method than does corn oil, although both oils are the same price.

In social science literature, the household was symbolized by the hearth, and those who lived together also ate together. Although the relationship of the last household size did not result in significantly raised RR, the lifetime weighted household size did. Those who averaged smaller households in their lifetimes had RR values from 2.0 to 2.4, and the trend *P* values were also significant.

To see whether household size affected food frequency levels, Table 5 shows this relationship among the 137 nonsmoking controls. For all the fresh vegetables, fresh fruit, dried or fresh fish, and sauces and spices (except pickled vegetables), those with larger household sizes consumed these foods more frequently than did smaller households. These relationships were statistically significant in trend for fresh leafy green vegetables, fresh fish, dried or salted fish, smoked or cured meats and poultry, and fermented beans or fermented bean sauces.

The data on beverages indicated that milk and tea consumption did not vary by household size, but that alcohol consumption did. There was a slight trend ($p = 0.04$) of higher alcohol consumption among women living in larger households, although the actual frequency averaged less than once per month. Because alcohol consumption among "social drinkers" is usually confined to celebrations like marriages, this variable might reflect the fact that larger families would have more such occasions than smaller ones. This possibility seems corroborated by the fact that the consumption of Dim Sum was significantly more frequent per month in larger households (trend *P* value was 0.03), because this is an activity where the entire family usually gets together and eats out in a restaurant.

The results from the data on nutrient indexes such as β-carotene, retinol, calcium, vitamin C, and Good Diet were similar to the other data in Table 5, which showed larger households as more frequent consumers of these types of foods, especially calcium.

As would be expected, there was a high correlation between the last household size and lifetime weighted household size. Because household size is related to a higher consumption of foods found to reduce the risk for lung cancer, the lifetime weighted household size might be a surrogate measure of "past" dietary habits. To see the effects of combining this measure of past dietary habits with a food item that reflects current habits and is related to risk in this data set, Table 6 shows how combining the two variables gives an even better predictor of RR values. By use of the group with larger household size and more frequent consumption of fruit as the baseline of RR = 1.00 (left upper corner), it can be seen that the RR increased as lifetime weighted household size and/or fruit consumption decreased. The effects were most apparent among the infrequent fruit consumers, where the trend ($p = 0.01$) was significant as household size decreased; also the adjusted RR increased in a dose-response manner from 1.75 to 4.16 to 5.77 for large, medium, and small households, respectively.

The same analysis was done for each of the nutrient indexes, and Table 7 shows how this model indicated a dose-response relationship with the generalized Good Diet variable. As can be seen, the *P* values for the adjusted trends were statistically significant or nearly significant when either Good Diet decreased (up to down) or the lifetime weighted household size decreased (left to right). When the lifetime weighted household size was large, the deleterious effects of a "poor" diet were minimal. But when the household size was small, an

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 2. Food Frequency and Lung Cancer Relative Risks[a] by Histological Type

	Relative Risks by Frequency of Consumption[b]							
	Squamous plus small cell				Adenocarcinoma plus large cell			
	Low	Medium	High	Trend *P* Value	Low	Medium	High	Trend *P* Value
Food items/groups' (no. of cases/no. of controls)								
Cruciferous vegetables (A)	16/61	12/61	4/15		18/61	25/61	3/15	
RR1	0.98	0.74	1.00	0.212	1.48	2.05	1.00	0.788
RR2	0.77	0.68	1.00	0.174	1.21	1.82	1.00	0.772
Fresh leafy green vegetables (B)	2/15	9/44	21/78		10/15	13/44	23/78	
RR1	0.50	0.76	1.00	0.803	2.26 (1)	1.00	1.00	0.147
RR2	0.66	0.97	1.00	0.779	3.09 (2)	1.18	1.00	0.090
Carrots (A)	9/38	18/82	5/17		11/38	34/82	1/17	
RR1	0.81	0.75	1.00	0.370	4.92	7.05 (3)	1.00	0.107
RR2	1.06	0.90	1.00	0.437	6.69 (4)	11.02 (5)	1.00	0.056
Beans/legumes (A)	15/59	12/66	5/11		19/59	24/66	3/11	
RR1	0.56	0.40	1.00	0.179	1.18	1.33	1.00	0.818
RR2	0.32	0.27	1.00	0.122	0.57	0.81	1.00	0.891
Tofu/soy products (A)	5/25	17/70	10/42		12/25	29/70	5/42	
RR1	0.84	1.02	1.00	0.346	4.03 (6)	3.48 (7)	1.00	0.021
RR2	0.65	1.00	1.00	0.372	3.51 (8)	3.55 (9)	1.00	0.042
Fresh fruit (C)	8/22	8/23	16/92		10/22	13/23	23/92	
RR1	2.09	2.00	1.00	0.066	1.82	2.26 (10)	1.00	0.009
RR2	2.30	2.70 (11)	1.00	0.043	1.55	1.80	1.00	0.022
Fresh fish (B)	14/40	7/48	11/49		21/40	14/48	11/49	
RR1	1.56	0.65	1.00	0.320	2.34 (12)	1.30	1.00	0.075
RR2	2.02	0.75	1.00	0.295	3.61 (13)	1.40	1.00	0.032
Dried/salted fish (E)	13/69	12/34	7/34		26/69	11/34	9/34	
RR1	1.00	1.87	1.09	0.918	1.00	0.86	0.70	0.958
RR2	1.00	2.24	1.11	0.911	1.00	0.75	0.75	0.690
Smoked meat/poultry (E)	10/51	12/54	10/32		20/51	16/54	10/32	
RR1	1.00	1.13	1.59	0.096	1.00	0.76	0.80	0.289
RR2	1.00	1.27	1.74	0.064	1.00	0.75	0.79	0.419

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Spices and sauces (no. of cases/no. of controls)								
MSG at home (D)	22/88	6/21	4/27		34/88	8/21	4/27	
RR1	1.00	1.14	0.59	0.863	1.00	0.99	0.38	0.375
RR2	1.00	1.21	0.77	0.760	1.00	1.26	0.46	0.466
Fermented seafood sauces (G)	7/41	15/53	10/43		15/41	24/53	7/43	
RR1	1.00	1.66	1.36	0.130	1.00	1.24	0.44	0.113
RR2	1.00	1.34	1.56	0.137	1.00	0.93	0.30	0.070
Fermented beans/sauces (E)	7/47	18/49	7/41		18/47	20/49	8/41	
RR1	1.00	2.47 (14)	1.15	0.782	1.00	1.07	0.51	0.597
RR2	1.00	3.24 (15)	1.55	0.722	1.00	1.20	0.55	0.731
Chili, fresh and sauces (G)	18/85	3/17	10/34		27/85	12/17	7/34	
RR1	1.00	0.83	1.39	0.782	1.00	2.22 (16)	0.65	0.597
RR2	1.00	0.79	1.41	0.723	1.00	2.89 (17)	0.75	0.731
Pickled vegetables (E)	3/34	10/43	19/60		9/34	17/43	20/60	
RR1	1.00	2.64	3.59 (18)	0.328	1.00	1.49	1.26	0.706
RR2	1.00	2.26	3.90 (19)	0.247	1.00	1.04	0.99	0.918
Beverages (no.of cases/no. of controls)								
Milk (F) (1 cup)	14/69	10/25	8/43		21/69	14/25	11/43	
RR1	1.09	2.15	1.00	0.288	1.19	2.19	1.00	0.482
RR2	0.84	1.67	1.00	0.269	0.80	1.84	1.00	0.786
Any alcohol (no/yes)	20/108	12/29			34/108	12/29		
RR1	1.00	2.23		0.201	1.00	1.31		0.592
RR2	1.00	2.07		0.141	1.00	1.41		0.460
Any tea (no/yes)	12/52	20/85			15/52	31/85		
RR1	1.00	1.02		0.567	1.00	1.26		0.285
RR2	1.00	1.42		0.462	1.00	1.69		0.188

a: RR1, unadjusted odds ratio; RR2, odds ratio adjusted for age, no. of live births, and schooling (+/−). *P* value of trend by exact values of RR1 and RR2. $n = 225$ for all except: beans/legumes (224), MSG (224), and chili (223).

b: Gives 95% confidence intervals as follows (no. in parentheses): (1) 0.97–7.24, (2) 1.04–9.14, (3) 1.29–94.29, (4) 0.70–64.26, (5) 0.99–62.90, (6) 1.15–15.29, (7) 1.14–11.05, (8) 0.86–14.22, (9) 1.04–12.04, (10) 0.92–5.10, (11) 0.88–8.26, (12) 1.02–6.19, (13) 1.26–10.36, (14) 0.91–7.89, (15) 1.04–10.03, (16) 1.22–9.12, (17) 0.98–8.54, (18) 0.91–13.72, (19) 0.96–15.73.

c: For (A)–(G), definition of each level of consumption is given in text.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

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Table 3. Nutrient Levels and Lung Cancer Relative Risks[a]

Nutrient[c]	Average Frequency of Consumption per Month[b]									Trend *P* Value	
	Low			Medium			High				
	No. of Cases/ Controls	RR1	RR2	No. of Cases/ Controls	RR1	RR2	No. of Cases/ Controls	RR1	RR2	RR1	RR2
β-Carotene (H)[d]											
All subjects	23/32	1.16	1.37	31/50	1.00	1.00	34/55	1.00	1.00	0.212	0.265
Squamous + small cell	7/32	0.75	0.87	9/50	0.62	0.71	16/55	1.00	1.00	0.435	0.420
Adenocarcinoma + large cell	13/32	1.49	1.68	18/50	1.32	1.13	15/55	1.00	1.00	0.091	0.055
Retinol (I)[e]											
All subjects	33/34	2.14 (1)	2.41 (2)	31/50	1.37	1.33	24/53	1.00	1.00	0.018	0.023
Squamous + small cell	11/34	1.43	1.72	9/50	0.80	0.80	12/53	1.00	1.00	0.240	0.237
Adenocarcinoma + large cell	16/34	2.27 (3)	3.11 (4)	19/50	1.83	1.83	11/53	1.00	1.00	0.061	0.052
Calcium (J)[f]											
All subjects	28/36	1.32	1.35	30/50	1.02	0.85	30/51	1.00	1.00	0.016	0.028
Squamous + small cell	6/36	0.57	0.66	11/50	0.75	0.57	15/51	1.00	1.00	0.897	0.919
Adenocarcinoma + large cell	18/36	1.82	1.85	14/50	1.02	1.04	14/51	1.00	1.00	0.016	0.013
Vitamin C (K)[g]											
All subjects	29/30	1.96 (5)	2.11 (6)	28/44	1.29	1.16	31/63	1.00	1.00	0.009	0.015
Squamous + small cell	6/30	1.05	1.26	14/44	1.67	2.27 (7)	12/63	1.00	1.00	0.456	0.426
Adenocarcinoma + large cell	20/30	2.47 (8)	2.42 (9)	9/44	0.76	0.45	17/63	1.00	1.00	0.011	0.014
"Good diet" (L)[h]											
All subjects	29/28	2.11 (10)	2.31 (11)	30/50	1.22	1.28	29/59	1.00	1.00	0.001	0.002
Squamous + small cell	4/28	0.60	0.75	14/50	1.18	1.34	14/59	1.00	1.00	0.226	0.189
Adenocarcinoma + large cell	20/28	3.24 (12)	3.55 (13)	13/50	1.18	1.54	13/59	1.00	1.00	0.002	0.003

a: RR1, unadjusted odds ratio; RR2, odds ratio adjusted for age, no. of live births, and schooling (+/−). *P* value of trend by exact values of RR1 and RR2.

b: Gives 95% confidence intervals as follows (no. in parentheses): (1) 1.15-4.85, (2) 1.12-5.18, (3) 0.96-6.40, (4) 1.05-9.16, (5) 1.15-4.76, (6) 1.02-4.40, (7) 0.86-5.99, (8) 1.10-5.91, (9) 0.98-5.97, (10) 1.22-5.22, (11) 1.08-4.95, (12) 1.42-8.37, (13) 1.36-9.30.

c: For (H)-(L), definition of each level of consumption is given in text.

d: Subjects ate cruciferous veg. + fresh leafy green veg. + carrots + beans/legumes ÷ 4.

e: Subjects ate fresh fish + dry/salted fish + milk ÷ 3.

f: Subjects ate fresh fish + dry/salted fish + cruciferous veg. + fresh leafy green veg. + carrots + beans/legumes + tofu/soy products + milk + pickled vegetables ÷ 9.

g: Subjects ate cruciferous veg. + fresh leafy green veg. + fresh fruit + beans/legumes ÷ 4.

h: Subjects ate cruciferous veg. + fresh leafy green veg. + carrots + beans/legumes + tofu/soy products + fresh fruit + soup + milk + fresh fish ÷ 9.

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 4. Eating Habits and Relative Risks[a] for Lung Cancer

	Never Smoked[b]		
	No. of Cases/Controls	RR1	RR2
Years of Dim Sum[c]			
10	14/23	1.00	1.00
1-9	16/54	0.49	0.36
0	58/60	1.59	1.22
Trend *P* value		0.794	0.998
Times/month of Dim Sum[c]			
>15	15/30	1.00	1.00
1-15	15/47	0.64	0.52
<1	58/60	1.93	1.71
Trend *P* value		0.351	0.448
Frequency (times/wk) of home-cooked soup			
1+	54/84	1.00	1.00
<1	34/53	1.00	1.15
Trend *P* value		0.170	0.240
Corn oil for cooking			
Yes	9/36	1.00	1.00
No	79/101	3.13 (1)	2.65 (2)
Trend *P* value		0.005	0.025
Last household size[d] (no. of people)			
>7	23/38	1.00	1.00
4-6	43/73	0.97	1.01
3	22/26	1.40	1.41
Trend *P* value		0.334	0.545
Lifetime weighted average household size[e] (no. of people)			
>6	27/61	1.00	1.00
4.51-6	30/41	1.65	1.85
<4.5	31/35	2.00 (3)	2.36 (4)
Trend *P* value		0.019	0.009

a: RR1, unadjusted odds ratio; RR2, odds ratio adjusted for age, no. of live births, and schooling (+/−).
b: Gives 95% confidence intervals as follows (no. in parentheses): (1) 1.44–7.29, (2) 1.13–6.20, (3) 1.02–4.27, (4) 1.00–5.55.
c: Dim Sum, Cantonese style of cooking where small dishes of savory and sweet items are consumed with large amounts of tea in a restaurant.
d: No. of people living and eating together in a family.
e: Σ (No. of family members, multiplied by no. of years lived together from birth) divided by age.

indirect indicator of poorer dietary quality and variety in the past, then the effects of a poorer "current" diet led to higher adjusted RR of 3.9.

Discussion

This study attempted to see whether diet influenced the risk for lung cancer among Chinese females in Hong Kong who never smoked. The 88 patients and 137 district controls were interviewed about their current frequency of consumption of a list of food items and beverages in addition to certain social variables that would indirectly reflect on dietary habits or life-styles.

In terms of current consumption patterns, fresh fruit and fresh fish were found to confer protection to those who reported the highest frequencies of eating them. Those at the lowest tertile levels of consumption had adjusted RR values of 2.4 for fruit and 2.8 for fish. These risk patterns showed statistically significant trends of dose response.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 5. Food Habits and Last Household Size Among Control Subjects Who Never Smoked

	Frequency[a] of Consumption by Last Household Size			
	Large (≥ 6 people) (n = 66)	Medium (4–5 people) (n = 42)	Small (1–3 people) (n = 29)	Trend P value[b]
Food items/groups				
Cruciferous vegetables	2.70	2.52	2.41	0.176
Fresh leafy green vegetables	5.54	5.48	5.21	0.029
Carrots	2.83	2.74	2.79	0.775
Beans/legumes	2.54	2.74	2.45	0.915
Tofu/soy products	3.08	3.24	3.07	0.778
Fresh fruit	4.73	4.67	4.55	0.442
Fresh fish	5.11	4.90	4.93	0.051
Dried/salted fish	2.85	2.60	2.34	0.046
Smoked/cured meat/poultry	3.00	2.69	2.62	0.010
Spices and sauces				
Monosodium glutamate at home	2.08	2.17	1.31	0.106
Fermented fish/shrimp sauce	2.14	2.12	1.90	0.224
Fermented beans/sauces	3.02	3.12	2.31	0.001
Chili, fresh and sauce	1.89	2.00	1.48	0.509
Pickled vegetables	3.18	3.33	3.21	0.542
Beverages				
Milk (1 cup)	2.02	2.24	2.31	0.494
% Any alcohol	26%	19%	14%	0.044
% Any tea	61%	64%	62%	0.467
Eating habits				
Years of Dim Sum	6.32	2.81	6.34	0.142
Times/month of Dim Sum	19.92	12.95	14.42	0.026
Lifetime weighted household size	6.56	5.53	5.44	0.007
Nutrient indexes				
β-Carotene	3.40	3.37	3.21	0.185
Retinol	3.32	3.25	3.19	0.121
Calcium	3.32	3.31	3.19	0.061
Vitamin C	3.88	3.85	3.65	0.123
"Good diet"	3.58	3.59	3.49	0.330

a: Frequency categories for first 15 items were as follows: 0, never; 1, <1/month; 2, 1–3/month; 3, 1–4/week; 4, 5–7/week; 5, ≥2/day.
b: Trend significance level derived from regression on last household size.

When the cases were analyzed by histological type, it was a surprise to find that those with adenocarcinoma or large cell tumors were more affected by diet than those with squamous or small cell tumors. The P values for trends indicating protection from lung cancer were statistically significant, or nearly so, when the consumption of fresh leafy green vegetables, carrots, tofu/soy products, fresh fruit, and fresh fish increased among those with adenocarcinoma or large cell tumors. By comparison, only the consumption of fresh fruit was protective, whereas the consumption of smoked meats/poultry or pickled vegetables increased the risk for squamous or small cell tumors.

These findings contrast with those from other studies, which report that the protective effects of diet were only found for squamous cell tumors and not in adenocarcinomas (19,20) or were stronger in squamous cell tumors than in adenocarcinomas (16,24). Perhaps this is due to the fact that the subjects in those studies were mostly Caucasian males who had a previous history of active smoking.

In the same way, when the foods were grouped by those sharing larger amounts of certain

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 6. Relative Risks[a] for Lung Cancer by Fruit Consumption and Lifetime Weighted Household Size

	Lifetime Weighted Household Size[b]							
	Large (> 6 people)		Medium (4.5-6 people)		Small (< 4.5 people)		Trend *P* Value	
	RR1	RR2	RR1	RR2	RR1	RR2	RR1	RR2
Fruit intake								
More (≥ 5 Times/week)	1.00 (15/41)[c]	1.00	1.56 (16/28)	1.97	1.54 (13/23)	2.05	0.45	0.18
Less (< 5 Times/week)	1.64 (12/20)	1.75	2.94 (1) (14/13)	4.16 (2)	4.10 (3) (18/12)	5.77 (4)	0.01	0.01
Trend *P* value	0.04	0.02	0.03	0.02	0.56	0.38		

a: RR1, unadjusted odds ratio; RR2, odds ratio adjusted for age and schooling (+/-). *P* value of trend by exact values of RR1 and RR2.
b: Gives 95% confidence intervals (no. in parentheses) of RR1 and RR2 as follows: (1) 1.29-11.02, (2) 1.37-12.61, (3) 1.83-15.00, (4) 1.91-17.40.
c: No. of cases/no. of controls.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 7. Relative Risks[a] for Lung Cancer by Consumption of Fresh Foods and Lifetime Weighted Household Size

	Lifetime Weighted Household Size[b]							
	Large (>6 people)		Medium (4.5-6 people)		Small (<4.5 people)		Trend *P* Value	
	RR1	RR2	RR1	RR2	RR1	RR2	RR1	RR2
"Good diet"[c]								
More	1.00 (16/37)[d]	1.00	1.28 (15/27)	1.51	1.62 (14/20)	1.68	0.22	0.03
Less	1.06 (11/24)	0.94	2.48 (1) (15/14)	3.10 (2)	2.62 (3) (17/15)	3.94 (4)	0.11	0.02
Trend *P* value	0.12	0.10	0.10	0.03	0.10	0.04		

a: RR1, unadjusted odds ratio; RR2, odds ratio adjusted for age and schooling (+/−). *P* value of trend by exact values of RR1 and RR2.

b: Gives 95% confidence intervals (no. in parentheses) of RR1 and RR2 as follows: (1) 1.10-8.49, (2) 1.08-8.85, (3) 1.26-9.17, (4) 1.39-11.20.

c: Good diet, average frequency per month of the following: cruciferous vegetables, leafy green vegetables, carrots, beans/legumes, fruit, soy products, milk, fresh fish, and soup.

d: No. of cases/no. of controls.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

nutrients, foods with vitamin C, retinol, and calcium seemed to confer the most protection, especially to those with adenocarcinoma or large cell lung cancers. Studies in the US (20,22) did not find any effect of vitamin C on lung cancer risk, and no one has reported about calcium and lung cancer. Because the population in Hong Kong consumes different foods than western populations and because such traditional food items such as pickled vegetables and salted or preserved fish, meats, and poultry formed a large part of the cuisine before the advent of refrigeration, the local intake of *N*-nitroso compounds might be higher than those on Euro-American diets. Thus, the protective action of vitamin C would depend on the other components of the local diet which may act as cocarcinogens, and these effects would differ, according to the geographic or cultural context of the population.

The possible protective effects of calcium were interesting because a previous study on nutrient intakes of people in Hong Kong (31) showed that the calcium intake levels in this population were well below the current recommended dietary allowances. On the other hand, the local intake levels of protein, carbohydrates, phosphorus, iron, thiamine, and ascorbic acid were similar to the intakes of those in western countries. Physiologically, it is known that calcium ions (Ca^{2+}) act as intracellular messengers and help to mediate the growth of cells (32). A study by Garland and colleagues (33) reported that higher dietary intakes of calcium reduced the risk for colorectal cancer. The role of calcium in cancer needs further research, and its effects may be more pronounced in populations who are generally deficient of this mineral. It may also be difficult to discriminate whether it is the vitamin A precursors, carotenoids, in leafy green vegetables that are protective or calcium because in Hong Kong, and in other countries where people do not consume dairy products, vegetables may be a major source of dietary calcium. The Hong Kong study (31) found vegetables to be the second most important source of dietary calcium; the first was from poultry and fish products.

This study also looked at variables that directly or indirectly inferred attitudes toward healthy eating or were correlated with healthier eating patterns. People in households that used corn oil for cooking had significantly lower RR values than did those who used other types of oil. It is unlikely that the nutrient qualities of corn oil is conferring the 2.7–3.1 times reduction in risk found in this study. Corn oil was only recently introduced into Hong Kong and has been popularly consumed for about five years. It is possible that the use of corn oil reflected the household's attitude in modifying cooking behavior mostly for health benefits rather than for reasons of the palate. This is because the usual alternative, peanut oil, is the same price, is more fragrant, and is the traditionally preferred type of cooking oil. This is because peanut oil can reach hotter temperatures than corn oil and can therefore better seal in the juices of foods when stir-frying.

The dietary significance of household size was also explored, and it was shown that women in larger households had better diets than those in smaller households. In general, the variety of foods in the diet, and the frequency of consumption of fresh foods (e.g., fruit, vegetables, and fish), increased as the household size increased. This is because with more family members eating together, more dishes of food would be prepared for each meal, the labor of purchasing and cooking the food could be shared, and there would be more economic and psychological incentives to cook and eat together. For example, the general rule of planning a meal at home or ordering at a Chinese restaurant states that the number of dishes should equal the number of people eating together, plus a soup. Thus, the larger the numbers of people who eat together, the greater the number of dishes and, therefore, variety of foods in the diet.

From data collected on residence patterns since birth for each subject, the lifetime weighted household size was estimated. Because it is difficult to accurately gather information on dietary patterns 20, 30, or 40 or more years ago, the variable, lifetime weighted household size, could be used as a surrogate index of past dietary patterns. Specifically,

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larger household sizes would indirectly signify more variety of foods in the diet and greater frequencies of consuming fresh foods, both of which are known to be generally protective against cancer.

This index of past dietary patterns was analyzed in combination with each of the food items and groups elicited in the interviews. The results from lifetime weighted household size and fruit indicated that those subjects from smaller households and the less-frequent consumers of fruit were 4.1–5.8 times more likely to get lung cancer than those from larger households and who were more frequent eaters of fruit. The data were generally consistent in showing that as household size or fruit intake decreased, the RR increased in a dose-response manner.

Similarly, when the lifetime weighted household size was combined with the average consumption frequency per month of items that would constitute a Good Diet (i.e., cruciferous vegetables, leafy green vegetables, carrots, beans/legumes, fruit, soy products, milk, fresh fish, and soup), the trend P values for the adjusted RR values were all ≤ 0.10. It was clear that risks from a poorer current diet combined with an index of poorer past diet (i.e., smaller lifetime weighted household size) led to consistent increases in RR. The adjusted RR for medium and small lifetime weighted household sizes were 3.1 and 3.9, respectively. However, those subjects having a poorer current diet but a better past diet (larger lifetime weighted household size) had an RR value of around 1.00. This shows that better past diets could compensate for the effects of poorer current diets.

Conclusion

In conclusion, the results of this study were consistent with the findings of other retrospective case-control studies of lung cancer and diet by showing that the consumption of fruit and vegetables and food sources rich in vitamin A (β-carotene and retinol) were generally protective. Moreover, these results support the strong role of diet in lung cancer risk, especially among those without a history of active smoking. Unlike the ambiguities surrounding epidemiological studies on environmental tobacco smoke and lung cancer, in which our previous analysis among the same group of subjects (11,12) found unclear relationships, the analysis in this study found many statistically significant and dose-response results. Certain dietary items were strongly protective among Chinese women who never smoked; also, in contrast to all the other studies, the effects of diet were mostly confined to lung tumors of the adenocarcinoma or large cell types.

This report also attempted to develop the idea that the lifetime weighted household size could be used as a surrogate measure of past dietary habits. Larger household sizes were correlated with more frequent consumption of fresh foods and a larger variety of foods. These consumption patterns are generally protective of cancer. However, the usefulness and validity of this index needs corroboration from other studies. But, with the exception of societies facing extremes of malnutrition and starvation (where larger household sizes are correlated with extreme poverty and deprivation), the correlation of larger household sizes with better diets might be applicable to other urbanized societies and may be useful in retrospective studies on diet and cancer.

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References

1. Hong Kong Cancer Registry: *Cancer Incidence in Hong Kong, 1982.* Kowloon, Hong Kong: Hong Kong Government's Medical and Health Department Institute of Radiology and Oncology, Queen Elizabeth Hospital, 1982.
2. Koo, LC, Ho, JH-C, and Lee, N: "An Analysis of Some Risk Factors for Lung Cancer in Hong Kong." *Int J Cancer* **35**, 149–55, 1985.
3. Koo, LC, Ho, JH-C, and Saw, D: "Active and Passive Smoking Among Female Lung Cancer Patients and Controls in Hong Kong." *J Exp Clin Cancer Res* **4**, 367–375, 1983.
4. Hirayama, T: "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer: A Study From Japan." *Br Med J* **282**, 183–185, 1981.
5. Trichopoulos, D, Kalandidi, A, Sparros, L, and MacMahon, B: "Lung Cancer and Passive Smoking." *Int J Cancer* **27**, 1–4, 1981.
6. Correa, P, Pickle, LW, Fontham, E, Lin, Y, and Haenszel, W: "Passive Smoking and Lung Cancer." *Lancet* **2**, 595–597, 1983.
7. Knoth, A, Bohn, H, and Schmidt, F: "Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen." *Med Klin Prax* **78**, 54–59, 1983.
8. Miller, GH: "Cancer, Passive Smoking and Nonemployed and Employed Wives." *West J Med* **140**, 632–635, 1984.
9. Garfinkel, L, Auerbach, O, and Joubert, L: "Involuntary Smoking and Lung Cancer: A Case-Control Study." *JNCI* **75**, 463–469, 1985.
10. Akiba, S, Kato, H, and Blot, WJ: "Passive Smoking and Lung Cancer Among Japanese Women." *Cancer Res* **46**, 4804–4807, 1986.
11. Koo, LC, Ho, JH-C, and Saw, D: "Is Passive Smoking an Added Risk Factor for Lung Cancer in Chinese Women?" *J Exp Clin Cancer Res* **3**, 277–283, 1984.
12. Koo, LC, Ho, JH-C, Saw, D, and Ho, C-Y: "Measurements of Passive Smoking and Estimates of Lung Cancer Risk Among Non-Smoking Chinese Females." *Int J Cancer* **39**, 162–169, 1987.
13. Koo, LC, Ho, JH-C, and Rylander, R: "Lifehistory Correlates of Environmental Tobacco Smoke: A Study on Non-Smoking Hong Kong Chinese Wives With Smoking vs. Non-smoking Husbands." *Soc Sci Med.* In press.
14. Committee on Diet, Nutr & Cancer, Assembly of Life Sciences, National Research Council: *Diet, Nutrition, and Cancer.* Washington, DC: National Academy Press, 1982.
15. Ames, BN: "Dietary Carcinogens and Anticarcinogens." *Science* **221**, 1256–1264, 1983.
16. Ziegler, RG, Mason, TJ, Stemhagen, A, Hoover, R, Schoenberg, JB, et al.: "Carotenoid Intake, Vegetables, and the Risk of Lung Cancer Among White Men in New Jersey." *Am J Epidemiol* **123**, 1080–1093, 1986.
17. Hirayama, T: "Diet and Cancer." *Nutr Cancer* **1**, 67–81, 1979.
18. MacLennan, R, Da Costa, J, Day, NE, Law, CH, Ng, YK, et al.: "Risk Factors for Lung Cancer in Singapore Chinese, a Population With High Female Incidence Rates." *Int J Cancer* **20**, 854–860, 1977.
19. Byers, T, Graham, S, Haughey, BP, Marshall, JR, and Swanson, MK: "Diet and Lung Cancer Risk: Findings From the Western New York Diet Study." *Am J Epidemiol* **125**, 351–363, 1987.
20. Byers, T, Vena, J, Mettlin, C, Swanson, M, and Graham, S: "Dietary Vitamin A and Lung Cancer Risk: An Analysis by Histologic Subtypes." *Am J Epidemiol* **120**, 769–776, 1984.
21. Samet, JM, Skipper, BJ, Humble, CG, and Pathak, DR: "Lung Cancer Risk and Vitamin A Consumption in New Mexico." *Am Rev Respir Dis* **131**, 198–202, 1985.
22. Hinds, MW, Kolonel, LN, Hankin, JH, and Lee, J: "Dietary Vitamin A, Carotene, Vitamin C and Risk of Lung Cancer in Hawaii." *Am J Epidemiol* **119**, 227–237, 1984.
23. Mettlin, C, Graham, S, and Swanson, M: "Vitamin A and Lung Cancer." *JNCI* **62**, 1435–1438, 1979.
24. Kvale, G, Bjelke, E, and Gart, JJ: "Dietary Habits and Lung Cancer Risk." *Int J Cancer* **31**, 397–405, 1983.
25. Shekelle, RB, Lepper, M, Liu, S, Maliza, C, Raynor, WJ, Jr, et al.: "Dietary Vitamin A and Risk of Cancer in the Western Electric Study." *Lancet* **2**, 1185–1189, 1981.
26. Gregor, A, Lee, PN, Roe, FJC, Wilson, MJ, and Melton, A: "Comparison of Dietary Histories in Lung Cancer Cases and Controls With Special Reference to Vitamin A." *Nutr Cancer* **2**, 93–97, 1980.
27. World Health Organization: "The World Health Organization Histological Typing of Lung Tumours, 2nd Edition." *Am J Clin Pathol* **77**, 123–136, 1982.
28. Breslow, NE, and Day, NE: *Statistical Methods in Cancer Research.* Lyon, France: IARC, 1980. (IARC Sci Publ No 32.)
29. Lubin, JH: "A Computer Program for the Analysis of Matched Case-Control Studies." *Comp Biomed Res* **14**,

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138–143, 1981.
30. Koo, LC: "The Use of Food to Treat and Prevent Disease in Chinese Culture." *Soc Sci Med* **18**, 757–766, 1984.
31. Newcombe, K: "Apparent Consumption and Socio-Economic Distribution of Nutrients in an Urban Settlement: Hong Kong." *Ecol Food Nutr* **6**, 9–22, 1977.
32. Rasmussen, H: "The Calcium Messenger System." *N Engl J Med* **316**, 1094–1101, 1986.
33. Garland, C, Shekelle, RB, Barrett-Connor, E, Criqui, MH, Rossof, AH, et al.: "Dietary Vitamin D and Calcium and Risk of Colorectal Cancer: A 19-Year Prospective Study in Men." *Lancet* **1**, 307–309, 1985.

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LIFE-HISTORY CORRELATES OF ENVIRONMENTAL TOBACCO SMOKE: A STUDY ON NONSMOKING HONG KONG CHINESE WIVES WITH SMOKING VERSUS NONSMOKING HUSBANDS

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Abstract—Studies to evaluate the effects of environmental tobacco smoke (ETS, passive smoking) often use nonsmoking wives with smoking discordant husbands. To see whether there were differences in exposures and behavior patterns among never-smoked wives with never-smoked vs ever-smoked husbands, the life-history profiles of 136 ever-married women with mean age of 59 were analyzed on 97 quantifiable variables. Overall, the results demonstrated that wives with never-smoked husbands had 'healthier' lifestyles than wives with smoking husbands. The former were better off in terms of socio-economic status, more conscientious housewives, ate better diets, and had better indices of family cohesiveness. They also fared better in variables that reflected health status with lower frequencies of the following: miscarriages, abortions, inhaling through the mouth, chronic cough, and chest X-rays. The differences were usually largest when comparing wives of never-smoked vs heavily smoking (>20 cigarettes/day) husbands. The results indicate some correlates of passive smoking that can act as important confounders when evaluating health risks among families with smoking husbands.

Key words—passive smoking, Chinese, lung cancer, environmental tobacco smoke, heart disease

In recent years there has been increasing research on the possible detrimental health effects from exposure to environmental tobacco smoke (ETS) or passive smoking. With the results of Trichopoulous *et al.* [1] and Hirayama [2] indicating an increased risk for lung cancer among nonsmoking wives married to smoking vs nonsmoking husbands, there has been a number of studies suggesting, among others, that ETS also increases the risk for a range of cancers [3], heart disease [4], pulmonary function and growth among children [5, 6], and respiratory symptoms among exposed family members [7, 8].

Most of these studies defined exposure by asking the subject whether the spouse/parent had smoked (yes/no), their duration of smoking (in years), and the number of cigarettes smoked per day. Whether these questions really measure dosage levels among those passively exposed, or merely indicate the smoking status of the spouse/parent are still controversial issues [9]. Furthermore, it cannot be excluded that having a smoking family member is associated with other lifestyle habits which could act as confounders and increase the risk of disease formerly related to ETS [10, 11].

For example, ETS was found by Friedman's group [12] in the San Francisco area to be associated with increased alcohol intake, marijuana use, and hazardous occupations among the exposed subjects. Another study [13] found that smoking husbands had more sexual partners than nonsmoking husbands. Mantel [11] suggested that important differences could exist between *families* with a smoking husband and those without. It therefore seems appropriate to compare the life-history profiles of wives married to smokers and nonsmokers.

METHODOLOGY

Data collection

From 1981 to 1983, 200 female lung cancer cases and 200 female controls were interviewed as part of a retrospective study on lung cancer in Hong Kong [14, 15]. The control subjects were randomly selected from lists of household members who lived in the same districts and housing type (public or privately owned) as the cases. From among the 200 district controls, 136 women were identified as nonsmoking wives. Nonsmokers were defined as those who had never smoked more than 20 cigarettes in their life times, and wives were women who had ever been married. None of the subjects had remarried. The mean age of the 136 subjects was 59.3 (SD 9.9), of which 40 (29%) were widows, 3 (2%) were separated, and 3 (2%) were divorced.

Since most women married in young adulthood and lived with their husbands for a majority of their adult lives, it was considered that any effects on lifestyles and habits should still be apparent although their husbands might no longer be present. This material then comprises all ever-married women. Analysis using only currently married wives was also done but not shown here since the life-history profiles between the ever-married and currently married wives were not noticeably different.

The husband's smoking status, whether he was still cohabiting, separated, or dead at the time of interview, was defined by the usual number of cigarettes he smoked per day when he lived with his wife and was an active smoker. The 8 ex-smoker husbands were classified by the number of cigarettes they consumed when they were smoking.

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All subjects were interviewed in their homes by two females with college degrees in sociology and previous experience in survey research. They underwent extensive training in carrying out interviews for this study, which included role playing and sensitivity to nonverbal communication and probing techniques. All of their recorded results were checked to monitor for inter- and intra-interviewer and -interviewee consistency and ensure that the data were of high quality and loose ends had been properly explored. Sometimes this meant that subjects had to be recontacted. These quality control procedures were maintained because some of the questions in the interview were semi-structured.

In this type of retrospective study, it was deemed important that a proper framework with appropriate probes be developed by the interviewer to facilitate recall by the informant on exposures in the distant past. Simultaneously, the interviewee was being trained to think retrospectively. Since the life-histories of each subject would be different and their levels of education and recall varied, the probing language would have to be adjusted individually. A general framework was established early in the interview by asking about residential histories, i.e. since birth, where the subject had lived (province, city/village), what type of housing, the number of rooms, how many household members had lived together, etc. These questions were repeated for each change of residence up to the time of interview. With this time, place, and general socio-economic framework, the interviewer was able to describe a setting to help an interviewee's recall or double-check data for consistency when subjects were asked questions pertaining to marriage, birth of children, ETS exposures, fuel types used in the home, exposures to possible hazardous chemicals/occupation, diet, etc. To facilitate this active probing by the interviewer and reduce the duration of the interview, all conversations were tape recorded so that the interviewer would not have to think and record all the data simultaneously. Sparse notes were taken during the interview on key points and to establish the residential histories. Within a couple days after each interview, the data were transcribed onto cards. On an average, each interview lasted 1.5–2 hr.

Statistical analysis and operational definitions

Among the data that were collected, 97 variables were quantifiable and judged to be of possible interest in this study on life-history exposures among nonsmoking wives. The information was grouped into 7 topical sections: ETS exposures, demographic background, reproductive histories, home exposures and activities, personal habits and activities outside the home, medications and health history, and dietary habits. Mean values were calculated for each variable with the denominator being the total number of subjects in each group. Among the variables described as "__/month", "__/year", or "__/exposed", the denominator was limited to those who were exposed since this would indicate their intensity of exposure. The variable preceding these measurements would already give the percentage exposed in each group.

Chi-square tests and *t*-tests were performed when comparing the values among wives with never-smoked (NS) vs ever-smoked (ES) husbands, light smokers (LS), i.e. 1–20 cigarettes/day, vs heavy smokers (HS), i.e. 21+ cigarettes/day, never-smoked vs heavy smokers, and never-smoked vs light and heavy smokers. Only the *P*-values for the first will be presented in the tables. Statistically significant *P*-values of the others will be discussed in the text.

To see whether there were any trends among husbands who never-smoked, were light smokers or heavy smokers, regression coefficients, unadjusted and adjusted for age were done on each variable based on the number of cigarettes the husband usually smoked per day. There was usually little difference in the results of the unadjusted and adjusted trend tests; thus only the exact *P*-values for the former will be presented.

In the design of the study, it was noted that Chinese women, especially those of Cantonese origin, emphasized the consumption of various kinds of herbs and foods to balance their metabolic systems in terms of the 'hot' and 'cold' system and to replenish their stores of body energy [16]. Because the weather is usually hot in sub-tropical Hong Kong, the consumption of 'cooling' herbal teas is popular, especially in the hot summer months. The composition of these teas is slightly varied, but some dozen herbs are common to all and they have a strong bitter taste. One of the most commonly consumed types is called '24 herbs cooling tea'. Dang Gwei (*Angelica polymorpha*) and *Pak Fung Yuen* ('White Phoenix Pills') are Chinese medicines specifically for nourishing women, especially after the menses or giving birth. They are reputed to help restore the blood, regulate the menses, and act as tonics since menstruation and giving birth are seen as depleters of body energy stores. *Gei Ji* (*Fructus lycium*) is a general tonic that can be consumed by anyone. It is frequently added to pork bone or chicken soup to create a 'nourishing' tonic soup (*bo tong*) for the whole family. Vitamins were generally perceived as a Western type of tonic. These data were gathered in the study and presented here because they were culturally specific types of health promoting behavior.

When subjects were asked about their frequencies of consuming 15 different foods or food groups, the answers were originally coded into 6 mutually exclusive categories: never, less than 1/month, 1–3 times/month, 1–4 times/week, 5–7 times/week, and 2 or more times/day. These categories were converted into the average number of times these foods would be eaten per month, giving each of the above categories the following weights respectively: 0, 1, 2, 11, 26 and 61. Then these weights were assigned to each subject for each food item and the mean values were calculated accordingly.

RESULTS

There were 70 women whose husbands had never smoked (NS) cigarettes and 66 whose husbands had smoked (ES) them sometime during their married life together. Among the smoking husbands, 74% ($N = 49$) smoked 20 or fewer cigarettes per day and therefore were defined as light smokers (LS), whereas

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Table 1. Environmental tobacco smoke exposure of nonsmoking wives with nonsmoking vs smoking husbands

Exposure variable	Mean values* for wives					
		Smoking husband				
	Nonsmoking husband, $N = 70$	Light smoker, 1–20 cig/day, $N = 49$	Heavy smoker, >20 cig/day, $N = 17$	P-value†	All smokers, $N = 66$	Nonsmoking vs smoking husband, t-test or chi-square test P-value‡
At home						
Percent exposed to tobacco	31%	100%	100%	—	100%	—
Years exposed to tobacco	13.27	31.14	31.59	0.0001§	31.26	0.71
Hundred hours exposed to tobacco	53.38	216.88	252.07	0.55	227.65	0.0001
Percent exposed from parents	7%	8%	18%	0.38	11%	0.48
Years exposed to parental tobacco	24.20	45.75	21.00	0.94	35.14	0.07
Hundred hours exposed to parental tobacco	242.60	474.75	114.33	0.93	320.29	0.83
Percent exposed from husband	6%	100%	100%	—	100%	—
Years exposed to husband's tobacco	29.25	28.86	27.82	0.71	28.59	0.71
Hundred hours exposed to husband's tobacco	127.25	185.53	225.24	0.31	195.76	0.27
Percent with ≥1 child(ren) smoked at home	17%	18%	6%	0.46	15%	0.75
At work						
Percent exposed at work	9%	8%	12%	0.90	9%	0.92
Years exposed to tobacco	8.00	10.50	15.50	0.33	12.17	0.24
Hundred hours exposed to tobacco	104.33	208.50	85.50	0.71	167.50	0.06
From home and work						
Percent exposed from home and work	44%	100%	100%	—	100%	—
Years exposed to tobacco	15.35	31.47	32.06	0.0001§	31.62	0.44
Hundred hours exposed to tobacco	106.19	241.65	262.29	0.003§	246.97	0.17
Percent exposed to cigarettes	37%	100%	100%	—	100%	—
Years exposed to cigarettes	12.46	31.14	32.00	0.0001§	31.36	0.64
Hundred hours exposed to cigarettes	98.96	237.49	253.76	0.008§	241.68	0.41
Age first exposed to tobacco	49.07	21.20	21.23	0.0001§	21.21	0.0001

*Mean value for all subjects.
†P-value for trend by linear test on regression coefficient by number of cigarettes/day smoked by the husband, or chi-square test of wives with nonsmoking, light and heavy smoking husbands.
‡P-value by chi-square or t-test of exact values of wives with nonsmoking vs smoking husbands.
§P-value ≤ 0.05 for age adjusted trend.
‖From cigarettes and pipe.

26% ($N = 17$) were heavy smokers (HS) consuming more than a pack per day.

Environmental tobacco smoke exposures

To study its possible association with female lung cancer, the original study made detailed enquires into past exposures to tobacco smoke [14, 15, 17]. In this paper, 14 quantitative exposure variables were selected, using average years and hours of exposure as measurements of dose and intensity among the exposed (Table 1). We differentiated between tobacco smoke, which included that from cigars, pipes, or cigarettes, and smoke only from cigarettes. Exposure was only counted if the parent, husband, other cohabitants or coworker(s) had smoked in the same room as the subject. They were not counted during periods when the parent(s), husband or cohabitant smoked outside the home, lived elsewhere, or were deceased. All of the measurements of dose among wives with NS, LS and ES husbands were statistically significant in trend when amounts from the home plus workplace were summed.

It is noteworthy that in the home environment, some 31% of the wives with NS husbands still had some exposure to tobacco smoke. Among those exposed to ETS at home, there were significant trends of increasing years ($P = 0.0001$) with increasing cigarette consumption levels by the husband.

Wives with HS husbands were about twice as likely to have had one or more parents who smoked, and among those with smoking parents, the difference in years of exposure from them was of borderline significance ($P = 0.07$) as the wives with NS husbands averaged 24.2 years vs 35.1 years for those with ES husbands. However, it should be noted that the amounts of exposure, whether in years or hours, was two or more times higher among wives with LS husbands than among wives of HS or NS husbands.

Some 6% of the wives, i.e. 4 subjects, had husbands who had smoked pipes but not cigarettes during their married life together. Among wives with some cigarette exposure from their husbands, wives with HS husbands did not have statistically higher dosage levels based on years or hours of exposure, than wives with LS husbands.

In a society where the extended family system is still revered, and adult children are expected to take care of and live with their aging parents, questions were asked about the subject's exposure to the tobacco smoke from their children. It was unexpected that children of fathers who were NS or LS were two to three times more likely to smoke at home than those with HS fathers. We do not have data on the percentage of children who were smokers.

The amount of ETS from the workplace was very slight, with only 8–12% of all wives experiencing some exposure. This is because many of the work environments (e.g. textiles, sewing, electronics) did not allow it. Among those exposed at the workplace, there was a slight tendency for wives with NS vs ES husbands to have lower exposures in terms of years ($P = 0.24$) and hours ($P = 0.06$).

When the amounts of exposure from the home and workplace were combined, some 44% of the wives with NS husbands had had previous exposure to

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Table 2. Demographic profiles of nonsmoking wives with nonsmoking vs smoking husbands

Variable	Mean values* for wives					
	Nonsmoking husband, N = 70	Smoking husband				Nonsmoking vs smoking husband, t-test or chi-square test P-value‡
		Light smoker, 1–20 cig/day, N = 49	Heavy smoker, >20 cig/day, N = 17	P-value†	All smokers, N = 66	
Age	60.36	58.49	57.00	0.60	58.11	0.01
Percent family owning a car	17%	12%	12%	0.71	12%	0.41
Percent family owning a home	37%	33%	29%	0.79	32%	0.51
Years attend school	3.10	2.29	4.47	0.99	2.85	0.71
Years urban life	38.16	40.04	44.41	0.21	41.17	0.06
Years rural life	22.24	18.10	12.59	0.07	16.68	0.01
Age at marriage	21.33	22.06	24.00	0.04	22.56	0.30
Years in Hong Kong	37.83	36.53	31.76	0.09	35.30	0.69
Percent ever worked outside the home	90%	82%	70%	0.11	79%	0.07

*Mean value for all subjects.
†P-value for trend by linear test on regression coefficient by number of cigarettes/day smoked by the husband, or chi-square test of wives with nonsmoking, light and heavy smoking husbands.
‡P-value by t-test of exact values of wives with nonsmoking vs smoking husbands.

tobacco, and 37% to cigarette smoke. From these data among the exposed, it was estimated that about 81–99% of the total years and 93–98% of the total hours of tobacco exposure from the home and work environments came from cigarettes. Among wives with LS husbands, 92% of their total tobacco exposure came from their husbands, and this proportion was 87% among wives with HS husbands.

As would be expected, there were highly significant increasing trends of years or hours of exposure from tobacco or cigarette smoke, among wives with NS, LS and HS husbands.

Wives with ES husbands were first exposed to tobacco at around 21 years of age vs 49 years of age for those with NS husbands, and this difference was significant.

Demographic profiles

Table 2 shows the values for selected demographic variables. Wives with NS husbands averaged 2 years older ($P = 0.01$) than those with ES husbands. Three variables gave some indication of socio-economic status: percent of families owning a car, percent of families owning their own home, and the number of years each subject had attended school. For all three indicators, families with a NS husband tended to be slightly wealthier and their wives better educated than ES families. The percentages of families that owned both a car and a home were 13% for wives with NS husbands vs 5% with ES husbands, and this difference was of weak statistical significance (P-value = 0.09).

Wives with ES husbands usually spent most of their lives in urban areas (usually Hong Kong, Guangzhou, Shanghai, Beijing), married later, and were more likely to have spent their adulthood as housewives. In contrast, wives with NS husbands usually spent much of their childhood, early adulthood, and were married in rural areas (mostly in Guangdong Province), and were more likely to have had experience in working outside the home. These differences were most apparent in the years spent in rural life, age at marriage, and percent ever working outside the home, with P-values for the trends among those with NS, LS and HS husbands ranging from 0.04 to 0.11.

Reproductive and gynecological histories

There were some interesting differences in the reproductive histories of the wives (Table 3). The most outstanding one was that wives with ES husbands were more likely to have miscarriages or abortions, resulting in more instances of surgical dilatation and curettage (D & C). Wives with NS husbands were 1.5–2 times less likely to have a miscarriage/abortion or D & C than wives with ES

Table 3. Reproductive and gynecological histories of nonsmoking wives with nonsmoking vs smoking husbands

Variable	Mean values* for wives					
	Nonsmoking husband, N = 70	Smoking husband				Nonsmoking vs smoking husband, t-test or chi-square test P-value‡
		Light smoker, 1–20 cig/day, N = 49	Heavy smoker, >20 cig/day, N = 17	P-value†	All smokers, N = 66	
Number of pregnancies	4.90	5.73	5.29	0.66	5.62	0.05
Number of live births	4.40	5.12	4.06	0.87	4.85	0.09
Percent had ≥1 miscarriages/abortions	33%	43%	59%	0.12	47%	0.09
Percent had ≥1 dilatation and curettage	16%	35%	23%	0.06	32%	0.03
Age at menarche	15.96	15.63	16.00	0.99	15.73	0.41
Age at menopause	47.72	47.90	47.53	0.26	47.80	0.19
Percent with regular menstruation	84%	76%	76%	0.46	76%	0.21

*Mean value for all subjects.
†P-value for trend by linear test on regression coefficient by number of cigarettes/day smoked by the husband, or chi-square test of wives with nonsmoking, light and heavy smoking husbands.
‡P-value by chi-square or t-test of exact values of wives with nonsmoking vs smoking husbands.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 4 Home exposures and activities of nonsmoking wives with nonsmoking vs smoking husbands

Variable	Mean values* for wives: Nonsmoking husband, N = 70	Smoking husband: Light smoker, 1–20 cig/day, N = 49	Heavy smoker, > 20 cig/day, N = 17	P-value†	All smokers, N = 66	Nonsmoking vs smoking husband, t-test or chi-square test P-value‡
Cooking and heating fuels						
Years wood + grass	31.96	34.73	25.88	0.80	32.45	0.47
Years kerosene	19.34	19.84	19.76	0.89	19.82	0.90
Years liquid petroleum gas	7.06	6.90	5.47	0.50	6.53	0.97
Years charcoal	5.01	0.90	3.12	0.08	1.47	0.0001
Years cooking	36.13	36.16	30.06	0.41	34.59	0.03
Years washing clothes by hand	38.00	36.35	36.41	0.94	36.36	0.01
Years house cleaning	35.11	35.08	31.41	0.78	34.14	0.02
Years house painting extensive repairs	2.97	1.33	1.71	0.92	1.42	0.0001
Percent burnt incense	73%	84%	76%	0.38	82%	0.21
Years burner of incense	38.06	35.49	29.61	0.18	34.07	0.43
Percent burnt religious candle	61%	71%	70%	0.48	71%	0.23
Years burner religious candle	38.37	34.80	27.00	0.05	32.81	0.27
Percent used mothballs	94%	100%	100%	0.80	100%	—
Percent used insecticidal sprays	69%	78%	65%	0.46	74%	0.47
Percent burnt mosquito coil	26%	27%	35%	0.72	29%	0.69
Years burner of mosquito coil	10.28	7.77	3.33	0.18	6.37	0.01

*Mean value for all subjects

†P-value for trend by linear test on regression coefficient by number of cigarettes/day smoked by the husband, or chi-square test of wives with nonsmoking, light and heavy smoking husbands

‡P-value by chi-square or t-test of exact values of wives with nonsmoking vs smoking husband

husbands, and there was a significantly increasing trend ($P = 0.06$) with increasing number of cigarettes smoked by the husband for D&C. Most of the abortions were actually miscarriages, as the common Chinese term includes both concepts. In this age group, only a few reported induced abortions as a method of birth control. In traditional ideology, greater numbers of children meant greater fortune. Women with ES husbands also tended to have more pregnancies.

Among the three variables reflecting the woman's menstrual patterns, i.e. the age it began, the age it stopped, and its regularity, no differences were apparent among the wives.

Activities and exposures in the home

The results from the comparative histories of these exposures (Table 4) have to take into account that wives with NS husbands tended to be 2–3 years older than those with ES husbands. Thus one would expect the former group to have longer durations of exposure for many of these variables.

To assess sources of indoor air pollution, subjects were asked about their duration of usage of various types of fuels for cooking and heating. Wives with NS husbands were significantly exposed to more years of charcoal than those with ES husbands.

Among other activities typical of Chinese housewives, the mean values were significantly higher among wives with NS vs ES husbands in their durations of cooking, washing clothes by hand, housecleaning and house painting/repairs. Most of these differences can probably be attributed to the older age of the wives of NS husbands. However, wives with HS husbands spent on average 30.1 years in cooking vs 36.1 years among wives with NS husbands, and this difference (6.1 years) is greater than their differences in age (3.4 years).

Table 5 Personal habits and activities outside the home of nonsmoking wives with nonsmoking vs smoking husbands

Variable	Mean values* for wives: Nonsmoking husband, N = 70	Smoking husband: Light smoker, 1–20 cig/day, N = 49	Heavy smoker, > 20 cig/day, N = 17	P-value†	All smokers, N = 66	Nonsmoking vs smoking husband, t-test or chi-square test P-value‡
Percent regularly inhaled through mouth	3%	10%	12%	0.19	11%	0.07
Percent snored when sleeping	14%	20%	12%	0.58	18%	0.54
Percent regularly worshipped at temple	36%	55%	41%	0.11	52%	0.06
Years worshipper at temple	30.44	31.78	22.86	0.17	29.94	0.54
Times year worshipped at temple	3.16	2.26	2.00	0.11	2.21	0.17
Percent regularly played majong	27%	28%	41%	0.52	32%	0.55
Years player of majong	8.53	8.64	9.57	0.67	8.95	0.90
Times month played majong	9.63	10.92	14.71	0.30	12.25	0.64
Percent regularly ate *dim sum* lunch breakfast	61%	57%	29%	0.06	50%	0.18
Percent regular physical exercise	39%	31%	35%	0.67	32%	0.41

*Mean value for all subjects

†P-value for trend by linear test on regression coefficient by number of cigarettes/day smoked by the husband, or chi-square test of wives with nonsmoking, light and heavy smoking husbands

‡P-value by chi-square or t-test of exact values of wives with nonsmoking vs smoking husbands

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Other sources of possibly hazardous fumes, smoke, and chemicals in the home typical of this cultural-geographical area were investigated. The percentages of those engaged in these activities: burning of incense (73–84%) and candles (61–71%) for ancestor and religious worship, and the use of mothballs (94–100% used some) and insecticidal sprays (65–78%), showed that these exposures were almost ubiquitous among all groups.

Although there were no significant differences in the percentages of those who burned (yes/no) incense or candles for religious or ancestor worship, the duration in years of such burning was always shortest among wives with HS husbands, and this trend was significant for religious candles ($P = 0.05$).

From 26 to 35% of the wives reported previous use of mosquito coils, which were usually burned 3–4 months per year during the summer months. Among the exposed, the 18 wives with NS husbands were significantly exposed to more years of mosquito coil (10.3) than the 19 wives with ES husbands (6.4).

Personal habits and activities outside the home

Various personal habits and activities outside the home were studied (Table 5). As an indication of respiratory habits, subjects were asked whether they had, for any periods of time greater than a few months and not due to a current cold/flu infection, inhaled primarily through their mouth and whether they snored during sleep. Three percent of the wives with NS husbands vs 11% with ES husbands were mouth inhalers ($P = 0.07$), indicating possible obstruction of their nasal passages. No significant differences were observed in rates of snoring although this habit has been associated with hypertension and heart disease [18, 19].

Although wives with ES husbands were more likely to visit temples or churches than wives of NS husbands ($P = 0.06$), wives with HS husbands consistently were the least frequent observers of religious activities by having the lowest figures for years and number of times/year they visited religious temples. On the other hand, they were the most likely to be regular gamblers by playing majong for more years and times per month than any of the other wives.

Dim sum is a Cantonese type of meal usually consumed at breakfast or lunch, where small portions of savory and sweet dumplings, meats, seafoods, etc. are served and consumed with large amounts of tea. Elderly women would usually go with family members to eat this, so it was an indirect sign of family cohesiveness. Wives with HS husbands were about half as likely to regularly eat *dim sum* as wives with LS or NS husbands, and the percentages increased as the husband smoked fewer cigarettes (chi-square P-value = 0.06).

Medications and health history

A comparison of their habits in taking Chinese herbal tonics/teas and patent medicines, and their history of respiratory symptoms is shown in Table 6. For most of the herbal tonics and 'cooling' teas, wives of HS husbands had among the higher percentages of being consumers. However, their duration in years, and frequency in times/year of consumption of the tonics and 'cooling' teas were always the lowest figures among the three groups of wives, with the exception of *Dang Gwei*. This exception may have arisen from their perceived need to supplement their bodies as a result of their higher frequency of unsuccessful pregnancies since the use of food tonics for this purpose is usually prescribed in this society [16].

Yet, on the other hand, the duration and frequency of consumption of these herbal tonics, teas and vitamins were, with the exception of years/drinker of 'cooling' teas, always the highest for wives with LS husbands. Thus, in the comparison of wives with NS vs ES husbands (where wives with HS husbands formed only 26% of those with ES husbands) the

Table 6 Histories of medication and past health of nonsmoking wives with nonsmoking vs smoking husbands

Variable	Mean values* for wives					
	Smoking husband					
	Nonsmoking husband, $N = 70$	Light smoker, 1–20 cig/day, $N = 49$	Heavy smoker, > 20 cig/day, $N = 17$	P-value†	All smokers, $N = 66$	Nonsmoking vs smoking husband, t-test or chi-square test P-value‡
Percent took *Pak Fung Yum*	11%	10%	18%	0.71	12%	0.90
Percent took *Dang Gwei*	43%	39%	65%	0.17	45%	0.76
Years/taker of *Dang Gwei*	9.83	15.05	14.00	0.31	14.67	0.16
Times/year took *Dang Gwei*	14.35	23.79	14.82	0.85	20.50	0.05
Percent took *Gei Ji*	70%	67%	76%	0.78	70%	0.97
Years/taker *Gei Ji*	15.37	18.33	10.38	0.35	16.09	0.99
Times/year took *Gei Ji*	17.36	21.66	12.85	0.93	19.27	0.02
Percent took vitamins	9%	14%	12%	0.62	14%	0.35
Percent drank 'cooling' herbal teas	40%	55%	41%	0.25	52%	0.18
Years/drinker 'cooling' teas	21.11	19.41	16.43	0.81	18.79	0.86
Times/year drank 'cooling' teas	18.25	22.00	12.50	0.64	19.89	0.004
Percent frequently took patent medicine for colds, cough, headache, pain	11%	8%	18%	0.55	11%	0.88
Percent with previous chest radiographs	48%	49%	59%	0.74	52%	0.73
Number of chest radiographs/person	3.85	5.71	7.00	0.31	6.09	0.01
Percent with chronic sputum	9%	8%	18%	0.48	11%	0.69
Percent with chronic cough	14%	4%	29%	0.02	11%	0.52

*Mean value for all subjects

†P-value for trend by linear test on regression coefficient by number of cigarettes/day smoked by the husband, or chi-square test of wives with nonsmoking, light and heavy smoking husbands.

‡P-value by chi-square or t-test of exact values of wives with nonsmoking vs smoking husbands.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Table 7. Dietary habits of nonsmoking wives with nonsmoking vs smoking husbands

Variable	Mean values* for wives					
		Smoking husband				
	Nonsmoking husband, $N = 70$	Light smoker, 1–20 cig/day, $N = 49$	Heavy smoker, >20 cig/day, $N = 17$	P-value†	All smokers, $N = 66$	Nonsmoking vs smoking husband, t-test or chi-square test P-value‡
Frequency of consumption per month						
Cruciferous vegetables	2.91	1.88	2.35	0.71	2.00	0.001
Fresh leafy green vegetables	43.66	45.90	40.70	0.84	44.56	0.87
Carrots	3.29	2.82	1.53	0.31	2.48	0.0003
Beans, legumes	2.97	1.86	2.00	0.25	1.89	0.0001
Bean curd and soy products	5.07	4.78	4.59	0.63	4.73	0.42
Fresh fruit	25.94	26.31	25.29	0.80	26.05	0.19
Fresh fish, seafood	32.56	34.47	36.88	0.34	35.09	0.87
Dried salted fish, seafood	4.73	6.26	8.41	0.24	6.82	0.09
Cured smoked meat, sausage, poultry	3.81	4.20	5.18	0.45	4.45	0.25
Pickled salted vegetables	7.01	9.94	7.76	0.78	9.38	0.0001
Chili, fresh or sauces	1.94	4.61	5.65	0.17	4.88	0.0001
Fermented and salted bean products§	5.21	4.49	6.24	0.85	4.94	0.02
Milk totaling 1 cup	7.21	2.88	2.71	0.07	2.83	0.0001
Home cooked soup (*Bo-tong*)	9.46	7.59	13.23	0.07	9.04	0.05
Mean values for wives						
Percent used corn oil in cooking	31%	18%	24%	0.27	20%	0.12
Percent drank alcohol regularly	19%	27%	12%	0.36	23%	0.55
Years drinker of alcohol	3.23	8.63	3.53	0.34	7.29	0.0001

*Mean value for all subjects.

†P-value for trend by linear test on regression coefficient by number of cigarettes/day smoked by the husband, or chi-square test of wives with nonsmoking, light and heavy smoking husbands.

‡P-value by chi-square or t-test of exact values of wives with nonsmoking vs smoking husbands.

§e.g. bean sauce, bean paste, "black" beans.

latter were significantly more frequent consumers per year of *Dang Gwei*, *Gei Ji*, and 'cooling' teas.

When asked whether they never, seldom, or frequently consumed over-the-counter patent medicines for such common symptoms as cold, cough, headache, and pain, 18% of the wives of HS husbands, vs 11% of those with NS and 8% of those with LS husbands answered that they consumed these medicines frequently, although these differences were not statistically significant.

With the high prevalence of tuberculosis in Hong Kong, about half of the women remembered having had at least one chest radiograph in the past. Among those who had had previous chest radiographs, wives of ES husbands had significantly more of them than those with NS husbands, and the average number of chest radiographs increased with the amount of smoking by the husband, although this trend was not significant. With poor doctor–patient communication and large numbers of subclinical/untreated tuberculosis in Hong Kong, most women could not recall whether they had been diagnosed with tuberculosis, so that answers to this question did not produce useful results.

Questions on sputum and cough were asked to give an indication of bronchial irritation. To avoid symptoms that might have been the result of cold/flu, sputum production and coughing were counted positive only if their durations had been greater than 6 months. Women with HS husbands were twice or more likely to suffer from these respiratory symptoms than women with LS or NS husbands, and the percentages of those with chronic cough significantly increased with the cigarette consumption levels of the husband ($P = 0.02$).

In general, wives with ES husbands were statistically more frequent consumers per year of traditional herbs like *Dang Gwei*, *Gei Ji*, and 'cooling' teas than wives of NS husbands. Among all 3 herbal concoctions, the wives of LS husbands were always the most frequent consumers, and wives of HS husbands the least frequent consumers.

Dietary habits

Wives with NS husbands tended to consume cruciferous vegetables, carrots, beans/legumes, fermented and salted bean products, and bean curd more frequently per month than those with ES husbands (Table 7). These differences were statistically significant for the first four items. On the other hand, they reported eating fresh fish, dried and/or salted fish, and cured/smoked meats (e.g. sausage, ham, pressed salted duck) less often, in a dose–response fashion with increased smoking by the husband. In addition, spicier foods such as pickled/salted vegetables and chilis and chili sauces were statistically more commonly consumed by the wives with ES than the NS husbands.

Since adults in this population rarely drank milk by itself but added it to tea, coffee, malted milk or cocoa, they were asked about their frequency of drinking a cumulative total of 1 cup of milk. Wives with ES husbands were found to be significantly less frequent consumers of milk, and this trend increased with the number of cigarettes smoked by their husbands ($P = 0.07$).

Two variables gave an indication of the household's emphasis and attitude toward home cooking. The preparation of *bo tong*, a soup that required boiling for several hours, is time and energy consuming, but highly regarded by the Cantonese as a means of furnishing additional nourishment in the traditional sense of health. The use of corn oil in cooking (yes/no) was asked because it was recently

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

introduced with publicity that using corn oil, rather than lard, peanut, or rapeseed oil, is healthier. Those who used corn oil would show that they were aware of its benefits and acted upon it, although peanut oil produced more fragrant cooking and rapeseed oil is cheaper. For both of these indicators of concern for 'healthy' cooking, households with NS husbands fared better.

In the original interviews, a number of questions were asked about consumption of specific types of alcoholic drinks: Chinese wine, Chinese tonic wines, Chinese liquor, Western wines and Western brandy liquor. Drinkers were defined as those who consumed these drinks one or more times a week. Most subjects said that they were intolerant to alcohol or felt uncomfortable after drinking it. Some only drank during infrequent social occasions such as weddings or holidays where toasting was a matter of courtesy. The actual percentage of drinkers (12–27%) was low, and those who did so usually said that they drank various Chinese tonic wines for health reasons such as nourishing their blood. These tonic wines are tinctures produced by soaking tonic herbs such as ginseng or animal products such as deer antler, tiger bones, snakes, etc. in wine. In comparing wives of NS vs ES husbands, the former were less likely to be drinkers 19% vs 23% ($P = 0.55$) and those who drank did so for shorter durations, averaging 3.2 vs 7.3 years ($P = 0.0001$).

DISCUSSION

The results from this study showed that wives had different behavior patterns and exposures to possibly noxious substances in the environment, when they were classified according to their husbands' smoking habits. As would be expected, most of the measurements on dose of ETS from the home plus workplace were significant in trend when wives with NS, LS and HS husbands were compared. However, simple generalizations about exposure levels to passive smoking cannot be made based solely on the husband's cigarette consumption habits, when detailed analyses were done. Among the more important findings: (1) some 44% of the wives with NS husbands had been exposed to ETS at home or work, and among those with some exposure, their duration in years or hours were not significantly different at the $P \leq 0.05$ level than the duration among wives with ES husbands, and (2) the total exposure levels in terms of hours or years were not very different between wives with LS vs HS husbands.

In addition, it was found that wives whose parents had smoked were much more likely to marry a HS spouse, and the age at first exposure to ETS at home or work was greatly influenced by the spouse's smoking status. Wives with smoking husbands were first exposed at the mean age of 21, which is approximately the age of marriage, whereas wives with NS husbands were more than twice as old at first exposure, with a mean age of 49. The latter group's exposure usually occurred at the time when their adult sons began smoking at home. These data indicate that surveys, which are attempting to measure current levels of ETS in the environments of older women, should be careful in extrapolating the results because higher levels of current exposure in some subjects may not be indicative that this was true of their past.

Significant differences were found in the demographic backgrounds of the wives. Most noticeably, wives with ES husbands spent more of their formative years in cities, and their duration of urban residence increased with the higher cigarette consumption levels of their husbands. This might be expected, as it is generally known that city dwellers tend to smoke more than their rural counterparts, and women who lived in the cities during their young adulthood would be more likely to marry a smoking husband than rural women. However, whether early habits acquired in a rural setting, or spending one's childhood, adolescence, and young adulthood in a rural rather than urban environment, offer some protection to some of the diseases attributed to ETS, is still an open question.

Wives of HS husbands were about twice as likely to experience miscarriages than wives with NS husbands, and there was an increasing trend ($P = 0.06$) of higher percentages of wives experiencing surgical dilatation and curettage with the increased cigarette smoking habits of their husbands. In a society which values the birth of children, the finding that wives with ES husbands had on average, significantly more pregnancies (5.6) than women with NS husbands (4.9) may have indicated a compensatory behavior for the former group's larger numbers of unsuccessful pregnancies. Other aspects of the women's gynecological histories, i.e. the ages of menarche and menopause, and menstrual regularity showed no differences among the wives. This may suggest that the source of the miscarriages was from the husband, since smoking men have been suggested to have more sperm abnormalities than men who do not smoke [20].

In comparisons of exposure to cooking and heating fuels, wives with NS vs ES husbands were more likely to be exposed to charcoal ($P = 0.0001$), a fuel commonly used in rural areas in the past.

In terms of Chinese homemaking activities, wives with HS husbands spent the fewest years in cooking, housecleaning, burning religious incense or candles, burning mosquito coil, and using insecticidal sprays. These differences were most apparent in the years spent cooking and burning religious incense or candles, with wives of NS or LS husbands engaging in these activities for an average of 6–9 years longer than wives of HS husbands. One could perhaps generalize that wives with HS husbands were likely to be the least conscientious housewives.

This pattern was also exhibited in the results of their activities outside the home, with wives of HS husbands worshipping at Buddhist/Taoist/Christian temples/churches for the shortest number of years and the least frequent number of times per year, and the family going out to eat *dim sum* together the least frequently, but these wives had the highest percentages of regularly playing the gambling game, majong.

In terms of health behavior and activities directed towards the promotion of health, Chinese culture emphasizes the consumption of various herbal teas and tonics to adapt the body to seasonal changes and

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

to increase one's store of energy. Although wives with HS husbands had among the higher percentages of being consumers of these products, their frequency in terms of number of times per year and duration in years of consumption were always the lowest of the three groups of wives for general tonics such as *Gei Ji*, and the 'cooling' herbal teas. They did, however, have the highest percentage of women who consumed patent medicines for such everyday symptoms as colds, cough, headache, and pain. Furthermore, wives with ES husbands had higher frequencies for taking the gynecological tonics than those with NS husbands. This may have been related to their higher rates of miscarriages/abortions as this herb is used in treating and preventing such disorders.

As a general group, the wives of women with LS husbands seemed to be the most avid consumers of these herbal tonics, 'cooling' teas, and vitamins as they usually had among the highest frequencies and durations of consumption.

The interpretation of the wives' habits in taking these medications, and indeed, any of the traditional Chinese tonics and herbs, may be difficult since it may indicate that they are more, or perceive themselves to be more sick, or that they are more likely to engage in health seeking behaviors. That the former may be true for wives with HS husbands is indicated by their highest frequencies of having chest radiographs, chronic sputum production, and chronic coughing.

In terms of diet, wives with NS husbands ate a healthier diet. Their frequencies of consuming cruciferous vegetables, carrots, beans/legumes, and milk were significantly higher than that for wives of smokers. On the other hand, the latter were more frequent consumers of cured/smoked meat products, fish (fresh and preserved), pickled vegetables, and chilis chili sauces, which would imply a diet higher in cholesterol, sodium, and *N*-nitroso compounds. These dietary patterns seem reasonable, since it is known that smokers tend to have duller taste buds than nonsmokers, and thus desire more stimulating and spicier foods. In order to meet these preferences by their husbands, wives of smoking husbands would tend to prepare meals with these ingredients, and for the sake of convenience, eat the same foods as they serve their husbands.

According to the U.S. National Research Council's 1982 report on *Diet, Nutrition and Cancer* [21], fresh leafy green vegetables, carrots, fresh fruit and milk, were identified as being protective of cancer and dried salted fish, cured/smoked meats, fermented and salted vegetables, alcohol, etc. were associated with higher risk for cancer. Wives with HS husbands always consumed the least of the former and the most of the latter. Similarly, a vegetarian diet has been linked with reduced incidence of a whole range of diseases in another study [22].

CONCLUSION

Overall, it seemed that wives with NS husbands had 'healthier' lifestyles than wives of ES husbands. The former were slightly better off financially, had more years of education, were more conscientious housewives, ate better diets, and had better indices of family cohesiveness (*dim sum*, ancestor worship by burning incense at home, visiting temples).

By contrast, wives with ES husbands were more likely to have less healthy behaviors by engaging in gambling and drinking alcohol, having poorer diets (cured/smoked meats, salted/dried fish, pickled vegetables, spicier foods), and were less conscientious housewives in terms of running the household and placing emphasis on cooking healthy foods.

In variables that reflected health status, wives with ES husbands were more likely to have a history of miscarriages/abortions, inhaling through the mouth, and chest radiographs. Wives of HS husbands had higher rates of chronic respiratory symptoms like chronic coughing and sputum production, and had the highest rates of frequently taking patent medicines for various everyday ailments.

These differences in life-history correlates were usually greatest in the comparison of families with NS vs HS husbands and may help to explain why some population studies have shown that families with a smoking husband were at higher risk of having a range of respiratory and cardiovascular health problems, cancer, poorer growth rates [23], etc.

The results from this analysis show that caution should be exercised when interpreting data on ETS. It may not be the hazards of tobacco smoke that are being evaluated, but a whole range of behaviors that result from having a smoking husband, which may in turn increase the risk for certain diseases among their wives and children. This can be from direct contact, as it is known that smokers are more likely to have upper respiratory tract infections, which increases the likelihood that other family members would be similarly affected by cross infection [7]. It can also be indirect, as the husband's preference for certain activities, e.g. gambling, drinking alcohol, and foods may encourage his wife to act and eat similarly, or be due to "assortative mating" [9].

This study is relatively small, with a total sample size of only 136 never-smoked ever-married women who had originally been selected as 'healthy' controls in a case-control study of lung cancer. In spite of this, some patterns pointing to differences in life exposures and habits based on the smoking status of the husband were found. These results indicate that more studies are needed from other communities to see whether generalizations about the past exposures and behaviors of wives with NS vs ES husbands can be made, and their consequent effects on the health of their family members.

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REFERENCES

1. Trichopoulos D., Kalandidi A., Sparros L. and MacMahon B. Lung cancer and passive smoking. *Int. J. Cancer* 27, 1, 1981.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

2. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br. med. J.* 282, 183, 1981.
3. Sandler D. P., Everson R. B. and Wilcox A. J. Passive smoking in adulthood and cancer risk. *Am. J. Epidem.* 121, 37, 1985.
4. Garland C., Barrett-Connor E., Suarez L., Criqui M. H. and Wingard D. L. Effects of passive smoking on ischemic heart disease mortality of nonsmokers. *Am. J. Epidem.* 121, 645, 1985.
5. Berkey C. S., Ware J. H., Dockery D. W., Ferris B. G. and Speizer F. E. Indoor air pollution and pulmonary function growth in preadolescent children. *Am. J. Epidem.* 123, 250, 1986.
6. Berkey C. S., Ware J. H., Speizer F. E. and Ferris B. G. Jr. Passive smoking and height growth of preadolescent children. *Int. J. Epidem.* 13, 454, 1984.
7. Colley J. R. T. Respiratory symptoms in children and parental smoking and phlegm production. *Br. med. J.* 2, 201, 1974.
8. Kasuga H., Hasebe A., Osaka F. and Matsuki H. Respiratory symptoms in school children and the role of passive smoking. *Tokai J. exp. clin. Med.* 4, 101, 1979.
9. Burch P. R. J. Re: "Passive smoking in adulthood and cancer risk" *Am. J. Epidem.* 123, 368, 1986.
10. Friedman G. D. Re: "Passive smoking in adulthood and cancer risk". *Am. J. Epidem.* 123, 367, 1986.
11. Mantel N. Re: "Passive smoking in adulthood and cancer risk" *Am. J. Epidem.* 123, 367, 1986.
12. Friedman G. D., Petitti D. B and Bawol R. D. Prevalence and correlates of passive smoking. *Am. J. publ. Hlth* 73, 401, 1983.
13. Buckley J. D., Harris R. W. C., Doll R., Vessey M. P. and Williams P. T. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet* 2, 1010, 1981.
14. Koo L. C., Ho J. H-C. and Saw D. Active and passive smoking among female lung cancer patients and controls in Hong Kong. *J. exp. clin. Cancer Res.* 4, 367, 1983.
15. Koo L. C., Ho J. H-C. and Saw D. Is passive smoking an added risk factor for lung cancer in Chinese women? *J. exp. clin. Cancer Res.* 3, 277, 1984.
16. Koo L. C. The use of food to treat and prevent disease in Chinese culture. *Soc. Sci. Med.* 18, 757, 1984.
17. Koo L. C., Ho J. H-C., Saw D. and Ho C-Y. Measurements of passive smoking and estimates of risk for lung cancer among non-smoking Chinese females. *Int. J. Cancer* 39, 162, 1987.
18. Norton P. G. and Dunn E. V. Snoring as a risk factor for disease: an epidemiological survey. *Br. med. J.* 291, 630, 1985.
19. Koskenvuo M., Kaprio J., Telakivi T., Partinen M., Heikkila K. and Sarna S. Snoring as a risk factor for ischaemic heart disease and stroke in men. *Br. med. J.* 294, 16, 1987.
20. Evans H. J., Fletcher J., Torrance M. and Hargreave T. B. Sperm abnormalities and cigarette smoking. *Lancet* 1, 627, 1981.
21. Committee on Diet, Nutrition, and Cancer, National Research Council. *Diet, Nutrition and Cancer*. National Academy Press, Washington, D.C., 1982.
22. Dickerson J. W. T., Davies G. J. and Crowder M. Disease patterns in individual with different eating patterns. *J. R. Soc. Hlth* 105, 191, 1985.
23. Rubin D. H., Krasilnikoff P. A., Leventhal J. M., Weile B. and Berget A. Effect of passive smoking on birthweight. *Lancet* II, 415, 1986.

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Present and future of indoor air quality.
C.J. Bieva, Y. Courtois, M. Govaerts, editors

ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER: IS IT THE SMOKE OR THE DIET?

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INTRODUCTION

Worldwide epidemiological studies on the association of environmental tobacco smoke (ETS) and lung cancer in non-smokers have produced controversial results. There have been problems associated with measuring the amounts of past lifetime exposure, misclassification of ex-smokers and current smokers as non-smokers, reliability of hospital records for smoking and diagnostic data, the tendency of lung cancer patients or their relatives to emphasize exposure to ETS, gaining access to representative controls for comparison purposes, and identifying other risk factors for lung cancer that could act as confounders of the association. With these potential problems in mind, studies have been designed and conducted in Hong Kong to explore the role of ETS, diet, air pollutants, and respiratory illnesses on lung cancer risk among non-smoking females .

In some ways, the Chinese female population in Hong Kong are ideal subjects to study the role of ETS or other non-smoking risk factors on lung cancer incidence. This is because they are unusual in three ways:

1). They have very high rates of lung cancer. From the population-based Hong Kong Cancer Registry, the world age-adjusted incidence rate in 1984 was 26.8/100,100 (1). When this incidence rate is compared with that among women in 10 other countries, it can be seen in Figure 1 that Hong Kong's rates are among the highest in the world (2).

2). They have high prevalence rates of chronic bronchitis. A study of 314 non-smoking mothers of primary school children in Hong Kong found that 10.5% reported having symptoms of chronic cough or phlegm lasting $\geq$3 months versus only 0.4% of 243 mothers in Japan (3). The higher prevalence of these symptoms for the Hong Kong population was also found among the children, with the percentages being 12.8% versus 0.8% respectively. The implications of these findings for lung cancer incidence among non-smokers in Hong Kong is ominous, since symptoms of chronic bronchitis was found to increase risk for lung cancer, even among those with no history of smoking (4).

3). They have low rates of smoking. A study of 200 female lung cancer cases gathered from 8 centers in Hong Kong indicated that 44% of them had never-smoked any type of tobacco (4). The population attributable risk due to smoking was calculated to be only 36% for females, whereas this percentage was 95% for males in Hong Kong. From these data, it can be calculated that the incidence rate not due to smoking was about 17.2/100,000 in 1984 (5). In a comparative study of female lung cancer incidence rates by ethnicity and place of residence, it was found that Chinese women in general (Fig. 2), regardless of whether they resided in Hawaii, Shanghai, or Hong Kong, had about twice the non-smoking

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incidence rates of women from other ethnic backgrounds (Japanese, White, Hawaiians) living in different areas in the Pacific Basin region (6).

Fig. 1 Female Lung Cancer Incidence Rates

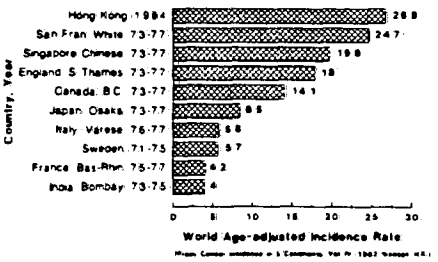
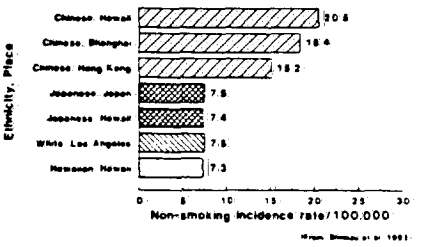


Fig. 2 Female Lung Cancer Incidence Rates not Attributable to Smoking



These data indicate that Chinese women living in different countries are exposed to some factor(s) that leads them to have non-smoking lung cancer rates about twice as high as other ethnic groups living in the same area. This would therefore rule out the effects of outdoor ambient air and occupational exposures (unless it was some special task that only Chinese women did) as a contributing factor. It is also unlikely to be genetic since China's world age-adjusted female lung cancer mortality rate was estimated to be only 4.75/100,000 for the entire country in 1973-75 (7). Thus the possible role of culture-specific agents, entering the body as inhalants or ingestants, which are causing the high rates of lung cancer and chronic bronchitis among Hong Kong Chinese women needs to be addressed.

ENVIRONMENTAL TOBACCO SMOKE

Among the most controversial, yet timely public health issues, is the possible role of ETS in the etiology of lung cancer or respiratory illnesses. From data collected in a retrospective study of 200 female lung cancer patients and 200 district matched controls in 1981-1983, Figure 3 shows the relationship between ETS exposure and risk for lung cancer among Hong Kong Chinese women with no history of smoking (4, 8-10). Dosage was defined as lifetime estimated hours of exposure to ETS from the home plus work environments, years of such exposure, and the daily number of cigarettes smoked by the husband. Only for husbands who smoked low numbers of cigarettes, i.e. $\leq$15/day, was the relative risk (RR) of 2.4 statistically significant (p=0.02). None of the the trends per variable were statistically significant. At the highest levels of exposure for all three measurements of dose, the RR ranged from 1.2 to 1.4. This might seem to agree with the conclusion of several recent reviews of epidemiological studies on ETS and lung cancer (11-13) that: "considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers....the risk of lung cancer is roughly 30% higher for nonsmoking spouses of smokers than it is for nonsmoking spouses of nonsmokers" (12, p.10). Yet, in our data, there was no

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dose-response relationship among any of the measurements of ETS, as the Mantel-Haenszel trend analysis p-values were all statistically not significant.

Fig. 3 ETS and Risk for Lung Cancer in Never-smoked Hong Kong Chinese Women

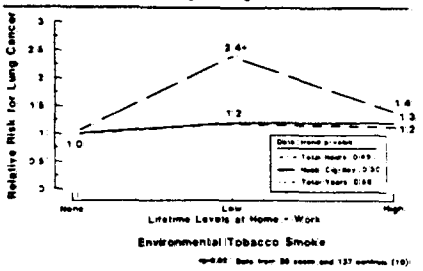
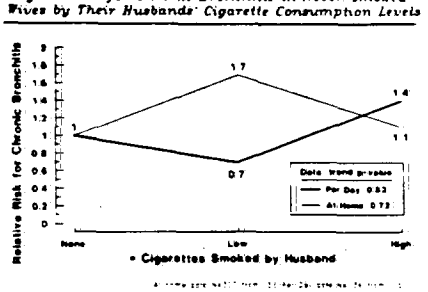


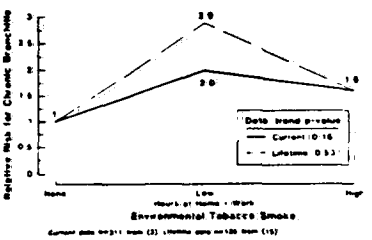
Fig. 4 Risk for Chronic Bronchitis in Never-smoked Wives by Their Husbands' Cigarette Consumption Levels



To study the relationship of ETS exposure to chronic bronchitis, non-smokers from two studies were used: 136 ever-married women who were controls from the lung cancer case-control study (10), and 311 mothers from a cross-sectional community study in 1985 (3). For risk of chronic bronchitis, which was defined as the presence of chronic cough or phelgm $\geq$ 3 months, the patterns were symmetrically opposed to each other depending on whether the wife's exposure was defined by the usual number of cigarettes her husband smoked at home, versus the number he smoked throughout the day (Fig. 4). The former should be a more accurate assessment of dosage for the wife since most of her contact with her husband's cigarettes would occur in the home environment. Yet both showed no dose-response effect with ETS. An even larger discrepancy was found when the duration (in months) of chronic bronchitis among wives was plotted against their husbands' cigarette consumption levels, defined as per day versus at home only. It was interesting that only the former showed a positive association (14).

The relationship is also unclear if the hours of ETS exposure from the home is defined as current versus lifetime hours of exposure, as shown in Fig. 5. The data on current hours comes from the cross-sectional study (3), and that on lifetime hours from the controls of the case-control study (10). The trend for current exposure hours (p=0.16) might suggest a relationship with ETS whereas that for lifetime hours did not (p=0.53).

Fig. 5 Risk for Chronic Bronchitis in Never-smoked Wives by Hours of ETS Exposure at Home + Work



With these inconclusive and sometimes contradictory results on the role of ETS and respiratory diseases among women with no

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history of smoking in Hong Kong, 3 questions come to mind:

1). If ETS increases the risk for lung cancer, shouldn't it also increase the incidence of other respiratory illnesses, e.g. chronic bronchitis, asthma, emphysema, that are associated with bronchial irritants and active smoking? As we have seen, the data for lung cancer was not statistically significant, and that for chronic bronchitis was conflicting depending on which measure of dosage was used. The more indirect measures of dosage, i.e. husband's daily cigarettes consumption levels, and the current hours of ETS exposure, gave more positive evidence of a relationship. But the more specific measures of duration, the number of cigarettes the husband smoked at home, and the lifetime hours of exposure did not suggest a dose-response effect with ETS. These inconclusive results are consistent with the world-wide data which show that children may have reduced lung function and increased respiratory symptoms when they have smoking parents, but these effects have not been observed among smoking discordant spouses (12). Our studies on respiratory symptoms in children have shown that the prevalence of such symptoms is strongly correlated with the reports of such symptoms among their mothers (3). Thus the association of ETS with childhood bronchitis and pnuemonia (13) might be due to cross infection from the mother or, more likely, smoking father to mother to child, rather than due to ETS itself. This is because it is known that smokers are more likely to have upper respiratory tract infections than nonsmokers, and the transmission of such agents is focused in the home environment for young children because their contact with extra-family members would be less than older children or adults.

2). Does the number of cigarettes smoked by the husband accurately reflect the amount of ETS exposure by the wife? Most of the studies on ETS and lung cancer defined the wife's exposure by the number of cigarettes her husband smoked per day. It was therefore assumed that wives of husbands who were heavier smokers (usually more than a pack of cigarettes per day) had concomitantly more ETS exposure than wives with husbands who were less avid smokers (less than a pack per day). Since we gathered data which allowed us to estimate lifetime ETS exposures in terms of years or hours, it was found that this assumption is questionable, as the amounts of these exposures in the past for nonsmoking wives with husbands who were light or heavy smokers were similar (15). In addition, our data showing conflicting interpretations of the relationship of ETS with the duration of chronic bronchitis if exposure is defined as the number of husband's cigarettes smoked at home versus throughout the day (14), highlights the need to be more specific about defining the wife's exposure levels if she has/had a smoking husband.

3). Since the increased risk of ETS and lung cancer is quite small, estimated by pooling all the studies to be about 30% (12), might the association really reflect the effect of other environmental factors that are associated with having a smoking husband? A comparative study of 97 quantifiable variables reflecting lifestyle patterns and environmental exposures found that nonsmoking wives with nonsmoking husbands generally had "healthier" lifestyles than those with smoking husbands (15). One of the most striking differences was the dietary patterns.

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Nonsmoking wives with nonsmoking husbands were more frequent consumers of cruciferous vegetables, carrots, beans/legumes, bean sauce, milk, and home made soup (Fig. 6). On the other hand, they consumed salted fish, pickled vegetables, chilis, and cured meats less than those with smoking husbands (Fig. 7). According to the report on Diet, Nutrition, and Cancer by the National Research Council (16), the former food items generally reduce cancer risk, and the latter increase it. The cogency of this association as an important confounder for studies associating ETS with lung cancer risk, is supported by our analysis showing diet to exert stronger and more consistent increases in lung cancer risk (17) than the data on ETS exposures among never-smoked women (10). Moreover, the food items which increased or decreased risk followed similar patterns as the correlations of nonsmoking wives with smoking or nonsmoking husbands, respectively. And finally, to go full circle, a recent comparison of the dietary patterns of nonsmoking Hong Kong Chinese women with and without chronic bronchitis, has suggested that chronic bronchitis is associated with a diet low in fresh fruit and high in cured meats and alcohol (5). Thus there is a common dietary linkage among the three risk groups of non-smoking Chinese women: those with chronic bronchitis, those with smoking husbands, and those with lung cancer.

Fig. 6 Dietary Habits of Nonsmoking Wives by Their Husbands' Smoking Status in H.K.

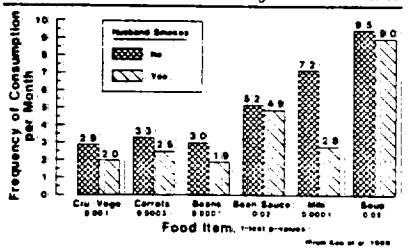
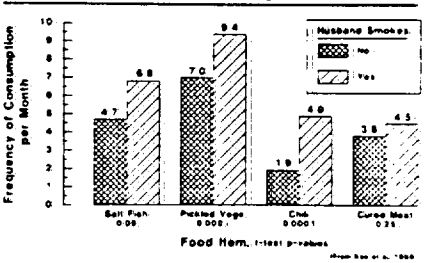


Fig. 7 Dietary Habits of Nonsmoking Wives by Their Husbands' Smoking Status in H.K.



OTHER INDOOR AIR POLLUTANTS

Since the natural inclination is to think of inhaled agents affecting respiratory diseases, we have also conducted studies on the role of cooking fuels (18), personal levels of exposure to nitrogen dioxide (19), urinary levels of cotinine (20) and hydroxyproline (21) adjusted for creatinine, and measured indoor levels of polycyclic aromatic hydrocarbons (22) and airborne levels of bacteria and fungi. Most of these data were collected as part of an ongoing collaborative comparative project with Japan (23). This is because the two areas have sharply contrasting incidence rates of female lung cancer and respiratory illnesses, with Hong Kong's female lung cancer incidence rates being 3 times higher, and chronic bronchitis prevalence rates about 10 times higher than that found in Japan (3). Although these studies are still in progress, the mean levels of these measurements of air pollution were not found to be significantly different between homes in Japan and Hong Kong.

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A study on lung cancer among Chinese females in Shanghai by Gao et al. (24) has suggested that greater exposure to cooking fumes was related to the higher risk for lung cancer in Chinese women. From data on our retrospective study of 88 never-smoked cases and 137 controls (10), the relative risk values suggested the opposite trend (Table 1). As women cooked for more years, their risk of lung cancer significantly decreased. These results are supported by other evidence on nonsmoking Chinese women in Hong Kong: wives with non-smoking husbands tended to cook for more years than those with husbands who were heavy smokers (15); women who were more concerned with healthy cooking habits, indicated by those who used corn oil for cooking, were significantly less at risk for lung cancer than those who used other types of cooking oil (17); and an analysis of the frequency of food consumption patterns between lung cancer cases and controls indicated that food habits provided substantially stronger evidence than ETS as being a risk factor for lung cancer in nonsmokers (10, 17). The contrasting results on the relationship of cooking activities with lung cancer risk between the Hong Kong and Shanghai data may have been due to their different definitions of cooking. The Hong Kong data defined it as years of cooking in the past, whereas the Shanghai data was based on current activities. Since it is known that the carcinogenic process of lung cancer takes decades, it would seem that an assessment of activities in the past would be more relevant than current behaviors.

TABLE 1
RISK FOR LUNG CANCER AMONG NEVER-SMOKED HONG KONG CHINESE WOMEN BY THEIR DURATION OF COOKING

Yrs.Cooking	#Case/#Cont.	Crude RR (95%CI)*	Adj. RR** (95%CI)
0-25	31/31	1.00	
26-40	29/59	0.49 (0.22-0.96)	0.38 (0.17-0.88)
41+	28/47	0.60 (0.24-1.13)	0.37 (0.14-0.96)
trend p-value:		0.16	<0.001

*95% CI from N:M matched analysis.
**N:M matching, adjusting for age, # live births, and schooling (+/-) as in (10).

DISCUSSION

Because Chinese females in Hong Kong with no history of smoking have high incidence rates of lung cancer, and high prevalence rates of chronic bronchitis, various studies have been conducted to evaluate the role of inhaled and ingested substances in their etiology. Data on lifetime exposures to environmental tobacco smoke did not show dose-response effects with risk for lung cancer. There were also inconsistencies when trying to see whether ETS was related to chronic bronchitis. If the wife's exposure was defined by her current hours of exposure or the number of cigarettes smoked by her husband per day, the data were suggestive of ETS increasing her risk for chronic bronchitis. However, if ETS was defined as lifetime hours of exposure, or the

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number of cigarettes smoked by the husband at home only, then no such relationship was found. How do we interpret such findings?

On the one hand, these conflicting results show that caution should be exercised when interpreting the results of various studies on ETS. Researchers, depending on their personal feelings on ETS and the fact that journals tend to accept submissions with clearly positive findings, may ignore the negative or unconsistent data and only publish the positive results if they have collected different ETS measurements and found them to be conflicting. This will result in ETS appearing in the published literature to be more consistently deleterious to health than might be the true situation.

We have also raised several questions about how such indirect measurements as the the husband's smoking habits might inaccurately reflect on ETS dosage for the wife and might be correlated with other lifestyle factors that would independently affect the risk for lung cancer among wives with smoking husbands. If ETS is causally related to lung cancer, it should also be related to excess risk for respiratory diseases commonly found in smokers, e.g. chronic bronchitis, asthma, and emphysema. The international and Hong Kong data linking ETS with even these diseases are unclear, and have only been found to be consistent among some studies on young children, where the role of cross-infection may be the factor rather than ETS itself (3).

Although domestic air pollutants like nitrogen dioxide may play a role in exacerbating respiratory illnesses, whether they are the key factor accounting for the 100% higher level of lung cancer incidence not attributable to smoking found among Chinese women is questionable. This is because the type of cooking and heating devices used by Chinese families in urban areas like Hong Kong, Singapore, Hawaii, and San Francisco are not unique to the Chinese population as the gas, electric, or kerosene appliances are used by all ethnic groups. In fact, because one of the most popular methods of Chinese cooking is the stir-fry method, the actual duration of time in which the stove is turned on (and therefore combustion is taking place) may be less than Caucasian families where roasting and baking for hours is commonplace. On the other hand, this Chinese method of stir-frying produces large quantities of oil droplets and smoke that accumulate in the kitchen air. Reports from Shanghai suggest that this may be the common factor increasing risk for lung cancer in Chinese women. However, our own data on cooking habits suggest the opposite: that the more the housewife cooks (in years); the more fresh foods like vegetables, fruit and fish are included in the meals; and if the housewife cooks in a manner which she believes is healthier for her family (use of corn oil and home-made soup); then there is a subsequent reduction in risk for lung cancer (17). Thus in our retrospective data, women who cooked for more than 25 years had about half the risk of lung cancer of those who cooked for shorter durations.

These results lead us to question the relative contribution of inhaled versus ingested substances in contributing to the high rates of lung cancer and chronic bronchitis in Hong Kong. Although air pollutants could certainly act as bronchial

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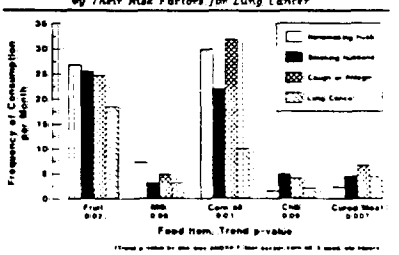
irritants, compensatory behavior was also found which may reduce the actual levels of inhaled substances. When family members smoked, there was an increased tendency to open windows so that the smoke would be dispersed outdoors (19). If stir-frying was done, ventilation fans would be used to channel the fumes outside, and kitchens were frequently located in balconies, or kitchen doors leading to other rooms in the home would be closed when cooking took place to prevent cooking fumes from entering other parts of the home. The role of domestic air pollutants also does not explain why children of primary school age (6-12 years old) in Hong Kong had rates of chronic bronchitis that were 10 or more times higher than children of similar age in Japan (3). There was no difference by sex of the child, and only about 15% helped in cooking. The levels of nitrogen dioxide measured by personal samplers among these school children were found to correlate closer with ambient outdoor levels than indoor activities related to combustion (19). These data, therefore, would lead us to suspect other culture-specific agents.

The most consistent thread is that of diet. If the diets of the lowest risk group, i.e. nonsmoking wives with nonsmoking husbands who did not have cough or phlegm (N=47), are compared with that of the three groups of non-smoking women who were at risk for respiratory disease, i.e. women with smoking husbands (N=69, 17 who had cough or phlegm were also included in the next group), women with cough or phlegm (N=38), and women with lung cancer (N=88), there was a dose-response trend with 5 dietary items (Figure 8). Wives without chronic bronchitis and married to husbands who did not smoke always consumed the healthier diet. This was characterized by more frequent consumption of fresh fruit, milk, and corn oil and less consumption of chili sauces/peppers and cured meats.

Fig 8 Dietary Habits of Never-smoked Women in Hong Kong by Their Risk Factors for Lung Cancer



Therefore, the evidence in Hong Kong suggests that ingestants may be the key factor explaining the high rates of lung cancer and chronic bronchitis among the never-smoked population. Since Chinese who emigrate overseas also retain their Chinese style of eating, this could be the culture-specific habit that explains the high rates of lung cancer also found among Chinese in Singapore, Hawaii, San Francisco, and Vancouver. To further support the possibility that it is certain food items i.e. ingestants, and not the cooking activities that produce inhalants that is important, studies in Hong Kong (8) and Singapore (25,26) have shown that even within the Chinese community, certain subcultures were more at risk for lung cancer than others. Women from the Chaozhou area in China were low at risk, Cantonese were higher, and women from the Danjia/Helao marine population were highest at risk (8). All basically use the same cooking techniques, but the components of the diet that make up their

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subcultural cuisines are different.

In conclusion, although inhaled substances like ETS or the by-products of domestic combustion may enhance bronchial irritation among nonsmokers, exposure to these types of air pollutants are not unique to Chinese households and cannot explain their excessive rates of lung cancer and chronic bronchitis. What is culturally specific and retained by Chinese, even when they emigrate overseas, is their diet. Data from Hong Kong suggests that vegetables, meats, and fish that are smoked, salted, cured, or pickled increased risk, whereas fresh versions of such foods and fruit reduced risk. Moreover, the former diet was more common among women with chronic bronchitis and wives with smoking husbands, whereas the latter diet was associated with wives with non-smoking husbands and without chronic bronchitis. Thus the controversy of ETS and lung cancer might be just a matter of "smoke", and the real culprit may be what is cooking over the fire for the etiological factors accounting for the excessively high lung cancer rates among non-smoking Chinese in Hong Kong.

ACKNOWLEDGEMENTS

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REFERENCES

1. Hong Kong Cancer Registry. Cancer Incidence in Hong Kong, 1984. Hong Kong Government's Medical and Health Dept. Institute of Radiology and Oncology, Queen Elizabeth Hospital, Hong Kong, 1984.

2. Waterhouse J, Muir C, Shanmugaratnam K, Powell J, Peacham D, Whelan S. Cancer Incidence in Five Continents, Vol. IV. IARC:Lyon, France. IARC Scientific Publications No. 42. 1982.

3. Koo LC, Ho JH-C., Matsuki H, Shimizu H, Mori T, Tominaga S. "A comparison of the prevalence of respiratory illnesses among nonsmoking mothers and their children in Japan and Hong Kong." Am Rev Respir Dis 138:290-295. 1988.

4. Koo LC, Ho JH-C, Lee N. "An analysis of some risk factors for lung cancer in Hong Kong." Int J Cancer 35:149-155. 1985.

5. Koo LC, Ho JH-C, Li KW. "Similarities in dietary risk factors among non-smokers with bronchitis and lung cancer." First Congress of the Asian Pacific Society of Respirology, Proceedings. (in press).

6. Shimizu H, Wu AH, Koo LC, Gao Y-T, Kolonel LN. "Lung Cancer in women living in the Pacific Basin Area." Natl Cancer Inst Monogr 69:197-201. 1985.

7. National Cancer Control Office of the Ministry of Health and Nanjing Institute of Geography of Academia Sinica. Atlas of Cancer Mortality in the People's Republic of China. Beijing:

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

China Map Press. 1980.

8. Koo LC, Ho JH-C, Saw D. "Active and passive smoking among female lung cancer patients and controls in Hong Kong." J Exp Clin Cancer Res 4:367-375. 1983.

9. Koo LC, Ho JH-C, Saw D. "Is passive smoking an added risk factor for lung cancer in Chinese women?" J Exp Clin Cancer Res 3:277-283. 1984.

10. Koo LC, Ho JH-C, Saw D, Ho CY. "Measurements of passive smoking and estimates of risk for lung cancer among non-smoking Chinese females." Int J Cancer 39:162-169. 1987.

11. U.S. Surgeon General. The Health Consequences of Involuntary Smoking. Washington, D.C.: U.S. Government Printing Office. DHHS(CDC)87-8398. 1986.

12. National Research Council. Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. Washington, D.C.:National Academy Press. 1986.

13. International Agency for Research on Cancer. Environmental Carcinogens, Methods of Analysis, and Exposure Measurement, Vol. 9, Passive Smoking. O'Neill IK, Brunnemann KD, Dodet B, Hoffmann D, eds. Lyon, France:IARC, Scientific Publications No. 81. 1987.

14. Koo LC, Ho JH-C. "Is there a threshold effect for ETS?: Results of data from never-smoked Chinese females in Hong Kong." Int Archives of Occupational and Environmental Health (in press).

15. Koo LC, Ho JH-C, Rylander R. "Life-history correlates of environmental tobacco smoke: A study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands." Soc Sci Med 26:751-760. 1988.

16. Committee on Diet, Nutrition, and Cancer, National Research Council. Diet, Nutrition, and Cancer. Washington, D.C.: National Academy Press. 1982.

17. Koo LC. "Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked." Nutr Cancer 11:155-172. 1988.

18. Koo LC, Lee N, Ho JH-C. "Do cooking fuels pose a risk for lung cancer?: A case-control study of women in Hong Kong." Ecology of Disease 2:255-265. 1983.

19. Koo LC, Ho JH-C, Ho CY, Matsuki H, Shimizu H, Mori T, Tominaga S. "Personal exposure to nitrogen dioxide and its association with respiratory illness in Hong Kong." (Manuscript in preparation).

20. International Agency for Research on Cancer. "International study on exposure to other people's smoke and urinary cotinine levels in non-smokers." Report in progress. Lyon,

2023381819

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France: IARC.

21. Matsuki H, Koo LC, Ho JH-C., Shimizu H, Mori T, Tominaga S. "A comparative study on the impact of environmental tobacco smoke on urinary hydroxyproline levels in Hong Kong and Japan." (Manuscript in preparation).

22. Kaku K, Matsushita S, Tominaga S, Koo LC. "Results of a pilot study on carcinogenic hydrocarbons in the indoor air at Kawasaki and Hong Kong." 29th Annual Meeting of the Japan Society of Air Pollution, Abstracts. Sendai, Japan. 1988.

23. Tominaga S, Tsuchiya E, Mori T, Matsuki H, Shimizu H, Ho JH-C, Koo LC. Saw D, Chan SH, Chan J, Kung ITM. "A study on the characteristics and etiology of lung cancer in Chinese females in Hong Kong." The Proceedings of Symposium on International Co-operative Study on Cancer in Asia and Africa. Monbusho Overseas Field Research - Special Cancer Study. Dept. of Preventive Medicine, Nagoya University: Nagoya, Japan. p.53-56. 1988.

24. Gao YT, Blot WJ, Zheng W, Ershow AG, Hsu CW, Levin LI, Zhang R, Fraumeni JF. Lung cancer among Chinese women. Int J Cancer 40:604-609. 1987.

25. Law CH, Day NE, Shanmugaratnam K. Incidence rates of specific histological types of lung cancer in Singapore Chinese dialect groups, and their aetiological significance. Int J Cancer 17:304-309. 1976.

26. MacLennan R, Da Costa J, Day NE, Law CH, Ng YK, Shanmugaratnam K. Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. Int J Cancer 20:854-860. 1977.

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Lung Cancer Risk and Mutagenicity of Tea

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To study the possible association between drinking tea and lung cancer, epidemiological and experimental materials were collected from the Chinese population in Hong Kong. In a retrospective study of 200 female lung cancer patients and 200 matched controls, all subjects were interviewed concerning their eating habits, smoking histories, and lifetime exposures to environmental pollutants. Analysis of the data demonstrated an adjusted and statistically significant increased lung cancer risk of 2.7 among those who drank green tea. Several brands of tea commonly drank in Hong Kong were assayed for mutagenicity using Ames' assay. Significantly elevated levels of mutagenic activity were found to be present after metabolic activation using cell-free extracts of cecal bacteria from rats. These data suggest that further research is needed to understand the possible consequences to human health of ingestants taken at low doses but long duration over the normal lifespan, and the possible interactive effect between mutagens in tea and other ingestants and inhalants in human cancer etiology. © 1990 Academic Press, Inc.

1. INTRODUCTION

The risk to develop lung cancer is commonly associated with inhaled agents. Yet recent toxicological research has demonstrated that the lung can be the site for uptake and metabolism of numerous substances which are administered by other means. For example, various pharmaceutical preparations given by the oral, intramuscular, intraperitoneal, or intravenous routes can accumulate in the lung, with subsequent toxic action. Cooper *et al.* (1986) reviewed around 40 different compounds which have been found to accumulate in the alveolar macrophages, pulmonary neutrophils, fibroblasts, alveolar type 2 cells, lymphocytes, and subepithelial glands. Examples of adverse reactions to such compounds are hypersensitivity, lung disease, capillary damage with following edema, fibrosis, and effects on the immune system in the lung.

Organic compounds given by oral or ip administration can be actively metabolised in the lung and potentially carcinogenic compounds such as benz[*a*]pyrene (B(a)P) can be absorbed from the gastrointestinal tractus or the peritoneum and deposited in the lung (Rylander *et al.*, 1989).

In view of the above, studies on lung cancer etiology should probably include ingested as well as airborne agents. Epidemiological as well as toxicological information is available on some such agents particularly fat (Wynder *et al.*, 1987) and tea.

Previous reports have shown that extracts of tea are mutagenic (Nagao *et al.*, 1979; Tamura *et al.*, 1980; Uyeta *et al.*, 1981) and epidemiological studies have found associations between tea drinking and lung cancer reported by Stocks

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(1970) in an international correlation study and Kinlen *et al.* (1988) in a case–control study. In a mortality study in the Tesside area, UK (Dean *et al.*, 1977), drinkers of six or more cups of tea a day had a significantly higher risk for lung cancer than those drinking one to five cups a day (RR 1.22 vs 1.00 for males ($P < 0.01$) and 1.65 vs 1.00 for females ($P < 0.01$)).

To further evaluate this relationship, an epidemiological and toxicological analysis of the association between tea drinking and lung cancer was performed. We used data from a case–control study of Chinese females in Hong Kong (Koo *et al.*, 1984) to evaluate the epidemiological association and samples of tea commonly consumed by that population to assay mutagenic activity using Ames' Salmonella assay.

2. MATERIALS AND METHODS

2.1 Population Study

From 1981 to 1983, a retrospective study on female lung cancer was conducted among the Chinese in Hong Kong (Koo *et al.*, 1984). A total of 200 female lung cancer patients from the wards or outpatient departments of eight hospitals and 200 female "healthy" controls matched by age and district of residence were interviewed to investigate their lifetime exposures to a variety of environmental agents. The dietary section of the interview inquired about the frequency of consumption of a list of food items or food groups. Cases were interviewed at hospital and asked to report on their usual food habits 1 year before their diagnosis of lung cancer or the appearance of symptoms. Controls were interviewed at home and asked to recall their current habits of eating. The mean age of the cases was 61.8 years (SD 10.0) and that for the controls was 60.6 years (SD 9.6).

In the question on usual liquid drunk during the day, the replies from the subjects were generally "plain boiled water" or a particular type of tea. Coffee was never recalled to be the main beverage drunk throughout the day for this age group.

Among the Chinese population in Hong Kong, fresh tea is usually prepared two to three times per day. About a teaspoon of dry tea leaves is put into a teapot or glass per person, and hot water is added. After steeping for a few minutes, the tea leaves fall to the bottom of the container and the tea infusion is ready for consumption. Hot water is continuously added to the container so that each portion of tea produces two to three cups of fluid. Green tea loses its flavor and color more rapidly than black tea. For an equivalent number of cups, more green tea leaves will be used. Normally, tea drinkers would sip four to nine cups of tea throughout the day.

In the analysis, those subjects who consumed dark fermented teas were grouped as "black tea" drinkers, and those who preferred the unfermented lighter colored teas were grouped as "green tea" drinkers. Table 1 describes subtypes of black and green teas, their origins, and their popularity in Hong Kong.

In calculating the risk for lung cancer, both crude and adjusted odds ratios (Breslow and Day, 1980) were estimated using the group who usually drank plain boiled water, i.e., the "no tea" group, as the baseline comparison group. The 95%

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TABLE I
CHINESE TEA SAMPLES USED IN HONG KONG AND INVESTIGATED IN THE MUTAGENICITY STUDY

Tea type	Brand	Origin	Remarks
Black	Luk-On (Orchid tea)	—	Inexpensive tea, commonly used among rural and working class households in Hong Kong
	Pu-erh	Yunnan	Heavily fermented brick tea with an ink-black color
	Ti Kuan Yin	Fujian	Light semifermented tea favored by connoisseurs in Fujian
Green	Swatow	Fujian	Green tea type common in Hong Kong
	Guizheu	Guizheu	Green tea drunk in Southwest China
	Lung Ching	Hangzhou	Connoisseur's green tea
	Jasmine	Variable	Green tea with added flowers from the Arabian jasmine plant (*Jasminum sambac*), commonly served in major cities in China and Hong Kong

confidence intervals of the odds ratios were derived from N:M matching of the subjects (i.e., unequal numbers of cases compared with controls in each strata (Breslow and Day, 1980)). Strata were defined by district of residence and housing type to minimize effects of socioeconomic background as confounders (Koo *et al.*, 1987). The adjusted odds ratios were calculated using a conditional logistic regression package, PECAN (Lubin, 1981), and adjusted for age (<50, 50–69, 70+), any formal schooling (yes/no), number of live births, average number of cigarettes smoked per day (0, 1–12, 13+), years of smoking (0, 1–40, 41+), and exsmoker status (yes/no). Forty-four percent of the cases and 68.5% of the controls had never smoked any form of tobacco.

To eliminate the possible confounding effects of other ingestants, odds ratios were calculated which adjusted for the previous demographic and smoking variables, and included alcohol intake (>1/week, yes/no) and frequency of consumption of fresh fruit and vegetables (the monthly frequency of cruciferous vegetables, fresh leafy green vegetables, carrots, beans/legumes, and fresh fruit summed for each subject and divided into tertiles). A more detailed report on the effect of diet on risk for lung cancer among women who have never smoked from this study has been reported previously (Koo, 1988).

2.2 Tea Samples and Extracts

The tea samples used in the mutagenicity test are found in Table 1. The infusions were prepared with 4 g black or green tea leaves which were soaked with 150 ml distilled water at 75–80°C (green tea) or 95–100°C (black tea) in porcelain cups covered with a saucer. After 3 min the infusions were separated from the leaves by passing them through Whatman No. 1 filter paper.

Each tea infusion was spin-frozen in an acetone/dry ice bath and freeze-dried under vacuum at approx 10^{-1} mbar overnight. The dry residues of four infusions of the same tea prepared simultaneously were pooled, dissolved in DMSO (E. Merck, Darmstadt, West Germany), with the 10-fold solvent volume of the equivalent dry residue weight and centrifuged at 5500*g* for 5 min at RT. The supernatant

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was stored at −75°C for a maximum of 2 months and was sterile filtered (0.45 μm pore size, Gelman, No. 4404) prior to the mutagenicity assay.

The tea infusions were also concentrated on XAD-2 resins basically according to Yamasaki and Ames (1977). The resulting dry residue was dissolved in 1 ml DMSO and was sterile-filtered prior to use.

2.3 Mutagenicity Assay

Salmonella typhimurium strains TA98 and TA100 (generously provided by Dr B. N. Ames, University of California, Berkeley, CA) were used to detect mutagens causing frameshift mutation and base-pair substitution, respectively. Preparation of the postmitochondrial (S9) fraction from livers of male Sprague–Dawley rats treated with Aroclor 1254 (Antechnika, FRG) was basically carried out according to Ames *et al.* (1975). An aliquot of 2 mg protein of this S9 per plate was found to activate 5 μg of B(a)P to induce approximately 800 TA98 revertants. Cell-free extract (CFE) of cecal bacteria was prepared from untreated rats according to Brown and Dietrich (1979) with the slight modification that cell lysis was performed by high pressure extrusion (French Press, Aminco). Rutin (Sigma, FRG), a glycoside of quercetin, which is only mutagenic after cleaving the glycosidic bond, was found to be activated by 0.25 ml CFE per plate to induce 3.1 + 0.2 rev./nmol in TA98 (mean + SE, $N = 8$).

The mutagenicity assay performed was a plate incorporation assay according to Maron and Ames (1983) using 0.25 ml of CFE and/or 0.25 ml of S9 mix (containing 45 μl of S9 fraction) or the equivalent amount of phosphate buffer, pH 7.4. Each test substance dose was assayed using four plates in each of the two independent experiments. After incubation at 37°C for 44 to 48 hr, colonies of bacteria reverted from histidine auxotrophy to prototrophy were counted automatically (Model 880, Artek Systems Corp., Farmingdale, NY). Colonies were controlled for true reversion by streaking on minimal glucose agar plates containing no histidine.

The mutagenicity was expressed as the regression coefficient calculated from the linear part of the dose–response curves over at least three doses from two independent experiments. All increases were significantly different from 0 (t test, $P < 0.002$, r = correlation coefficient).

3. RESULTS

3.1 Lung Cancer

Table 2 shows the relative risk for lung cancer from the case-control study on Chinese women in Hong Kong. Lung cancer risk was higher among tea consumers, and this was statistically significant for green tea, where the adjusted odds ratio was 2.7 ($P < 0.05$) after adjustment for smoking and demographic factors. There was little change in the risk ratios after adjustment for other dietary habits like alcohol and consumption of fruit and vegetables. This indicates that the tea consumption patterns were independent of these other dietary items. The possibility of recall bias accounting for this finding is negated by the fact that tea drinking was not suspected during the interviews to be a possible risk factor. The question on usual beverage drunk throughout the day was added to the interviews

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TABLE 2
RELATIVE RISK FOR LUNG CANCER BY TEA CONSUMPTION HABITS AMONG CHINESE FEMALES IN HONG KONG

Usual drinking liquid	No. of cases/ controls	Relative risk		
		RR1 (95% C.I.)[a]	RR2 (95% C.I.)[b]	RR3 (95% C.I.)[c]
Boiled water	72/75	1.00	1.00	1.00
Black teas	105/106	1.03 (0.75–1.69)	1.43 (0.88–1.35)	1.43 (0.88–2.33)
Green teas	23/13	1.84 (0.87–3.70)	2.67 (1.10–6.48)	2.74 (1.10–6.80)

[a] Unadjusted odds ratio.
[b] Odds ratios adjusted for age, No. of live births, schooling (%), and smoking habits.
[c] Odds ratio adjusted for all in RR2, plus alcohol drinking (%), frequency of consumption per month of fresh vegetables and fruit (low, medium, high).

for overall coverage on dietary patterns of the subjects, rather than to evaluate tea drinking per se.

3.2 Mutagenicity

Mutagenicity was detectable only in the presence of CFE. The response was enhanced by the addition of S9 mix (see Fig. 1). For an equivalent dose of approximately 0.2 ml of the original tea infusion per plate, the increase in mutagenicity was nearly linear. A maximum mutagenic response was obtained at a dose of 0.5 ml/plate with an increase factor of 2.2 to 3.6 in strain TA98 over the number of spontaneous revertants. At higher doses, no further increase occurred or the mutagenic response decreased. However, the application of water instead of DMSO as a solvent for the lyophilisate resulted in a lower dose-related increase in the mutagenicity (data not shown).

Table 3 reports the results from mutagenicity testing of tea extracts. On an infusion volume basis, all four brands of green and all three brands of black tea induced frameshift mutations in strain TA98. Strain TA100 was always less susceptible than strain TA98 (data not shown). Generally, higher mutagenic activity was observed in green teas. The total mutagenicity of one cup of green tea was found to be 8.3E4 revertants and that of black tea, 4.8E4 revertants in strain TA98.

Repeated infusions of one of the tea samples (Swatow) at time intervals of 30 min resulted in a decrease in the amount of water solubles from 188 to 75–36 mg/g, with corresponding decreases in mutagenicity from 876 to 282–311 revertants/ml. Tea infusions concentrated on XAD-2 resin caused a lower mutagenicity and recovery for teas with high mutagenic activity was only about 30%.

4. DISCUSSION

Lung cancer is the leading cause of cancer death among women in Hong Kong, and it is estimated that the majority of the cases (64%) are not attributable to a history of smoking (Koo *et al.*, 1985). Moreover, with an annual world age-

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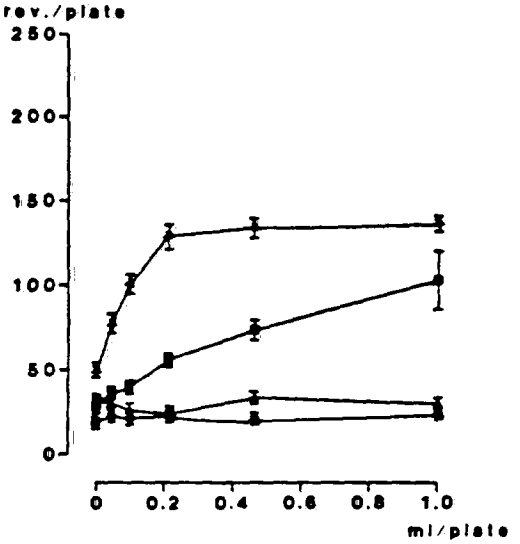

FIG. 1. Mutagenicity of green tea "Jasmine" in *Salmonella typhimurium* strain TA98. The dry residue of four tea infusions prepared from 4 g tea leaves and 150 ml distilled water per infusion were lyophilized and dissolved in small amount of DMSO. The equivalent amounts of tea infusions were assayed alone (●) and in the presence of S9 (▲), CFE (■), and S9 plus CFE(*). Values are expressed as the mean (SE) of four plates per dose. The spontaneous reversion of strain TA98 was 22(8) rev./plate (N = 12) and 6 μg of daunomycin-induced 1325(83) rev./plate (N = 8).

adjusted incidence rate of 27.1 per 100,000 for 1982, this ranked it to be among the highest in the world for women (Koo, 1988).

In previous epidemiological studies, research has focused on the role of inhaled agents such as environmental tobacco smoke (ETS) (Koo *et al.*, 1984, 1987) and cooking fuels (Koo *et al.*, 1983). When lifetime levels of such exposures were estimated, there were no major agent or dose differences in the exposure levels of cases and controls. This may be a result of little accumulation of air pollutants in homes, because the semitropical climate in Hong Kong necessitates that windows be continuously left open for most months of the year and centralized air conditioning is too expensive for most homes. Therefore the role of inhalants in lung cancer etiology among Hong Kong Chinese may differ from that of Chinese in other parts of China like Yunnan or Manchuria, where the use of smoky coal for heating and cooking generates large amounts of indoor air pollutants and has been found to be associated with increased risk for female lung cancer in Yunnan, China (Mumford *et al.*, 1987).

The role of ingestants in lung cancer risk among never-smoked Hong Kong Chinese women seemed to surpass that of inhalants. A diet high in fresh vegetables, fruit, and fish was found to reduce risk for lung cancer, whereas more frequent consumption of cured/smoked meats, pickled vegetables, and alcohol increased risk (Koo, 1988). Results from the present study suggest that tea may

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TABLE 3

MUTAGENICITY OF CHINESE TEA INFUSIONS IN *Salmonella typhimurium* TA98 IN THE PRESENCE OF CELL-FREE EXTRACT (CFE) OF CECAL BACTERIA AND THE POSTMITOCHONDRIAL (S9) FRACTION FROM AROCLOR-INDUCED RAT LIVER

Tea type	Brand	Mutagenicity		
		Revertant/ml	Correlation coefficient (r)	*P* value <
Black	Luk-On	421	0.77	0.001
	Ti Kuan Yin	342	0.87	0.001
	Pu-erh[a]	200	0.87	0.001
		Mean: 321	—	—
Green	Guizhou	647	0.95	0.001
	Swatow	490	0.86	0.001
	Lung-Ching	553	0.94	0.001
	Jasmine[a]	515	0.92	0.002
		Mean: 551	—	—

Note. *P* values from test for zero slope performed separately for each substudy.

[a] Assayed only in one substudy.

also independently increase risk for lung cancer. These data support the suggestive epidemiological findings of Stocks (1970) and Kinlen *et al.* (1988). It was also found that the brands of green and black tea commonly consumed by the population in Hong Kong contain a compound(s) which becomes mutagenic after metabolic activation. The mutagenic activity in one cup of tea infusion was found to be equivalent to approximately 0.3 mg of B(a)P for black tea and 0.5 mg for green tea.

The mutagenic activity was detectable only in the presence of a metabolizing system containing glycosidases and was enhanced by the addition of S9 mix. This result agrees with the findings of other authors (Nagao *et al.*, 1979; Tamura *et al.*, 1980; Uyeta *et al.*, 1981). Tea has also been shown to be carcinogenic in animals exposed to it orally, by injection, or by local application (Korpassy and Mosonyi, 1950; Kirby, 1960; Kaiser, 1967; Kapadia *et al.*, 1976; Bogovski and Day 1977).

Ames' Salmonella assay for detecting mutagenicity is able to predict carcinogenicity with a predictivity of 75% and with a false positive response (noncarcinogens giving a positive response) of 29% (Zeiger and Tennant, 1986).

In epidemiological studies, tea drinking has apart from lung cancer been associated with the risk of tumors in several organs (Stocks, 1970; Hartge *et al.*, 1983; McLaughlin *et al.*, 1983,1984; Kinlen and McPherson, 1984; Tajima and Tominaga, 1985; Heilbrun *et al.*, 1986; Jensen *et al.*, 1986).

In studying mutagenicity levels, infusions from green tea were slightly more active than those from black tea, although the differences were not large. Similarly, the epidemiological data showed a higher risk for lung cancer among green tea drinkers than black tea drinkers. Although the slightly higher mutagenicity of green tea could contribute to this difference, dosage is possibly also important. Green tea drinkers would be more likely to consume larger quantities of extracts

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from tea because green tea has a weaker flavor and color per weight than black tea, and therefore requires more tea leaves for the same number of cups. However, our findings are tentative, since only 23 cases (11.5%) and 13 controls (6.5%) claimed to be regular drinkers of green tea.

Thus we did not collect data on cups of tea drunk throughout the day and were therefore unable to perform a dose–response analysis. Also, because tea drinking is ubiquitous during social occasions and when eating in restaurants, even persons who preferred drinking boiled water may have been somewhat exposed to tea. The risk might thus have been slightly underestimated in this study.

It is not known which chemical compound(s) in the tea extract is responsible for its genotoxicity and carcinogenicity. Of the naturally occurring mutagens in food, the most ubiquitously distributed mutagens of plant origin are flavonoids. Among them, quercetin and kaempferol are commonly found in high concentrations in various vegetables and fruits (Brown, 1980). For green and black tea glycosides, a mutagenic effect has been reported after metabolic activation (Uyeta *et al.*, 1981). These effects were probably derived from the flavonols quercetin, kaempferol, and myricetin. The total concentration in tea of these substances is more than 10 g glycosides/kg (Herrmann, 1976). Other mutagens acting directly without metabolic activation, such as glyoxals, have also been found in black tea and a trace of them also in green tea (Nagao *et al.*, 1986). In this study, no direct acting mutagenicity was detectable. However, tannin-containing fractions of green tea leaves were recently found by microsomal degranulation technique to contain potential carcinogenic activity (Minocha *et al.*, 1986).

An association between tea consumption and the appearance of lung cancer in humans would require that the ingested active metabolites from the tea extract are transported to the lung. Studies on orally administered rutin show that tea-derived quercetin glycosides reached the lower bowel unaltered and that its β-glycosidic bond was hydrolyzed by the intestinal microflora (for review, see Brown, 1980). Derivatives of phenylacetic and phenylpropionic acid were detected as the first bacterial metabolites of rutin and were found to be excreted in the urine or absorbed and metabolized by the intestinal wall in only small amounts (Brown, 1980; Baba *et al.*, 1983; Brown and Griffiths, 1983). A high absorption from the intestinal tract was observed when [4-^{14}C]quercetin was administered orally to rats (Ueno *et al.*, 1983). Within 48 hr after administration, approximately 20% of the quercetin was absorbed and rapidly excreted into the bile and urine as glucuronide and sulfate conjugates. More than 30% decomposed to yield CO_2 and approximately 30% was excreted unchanged in the feces. Similar results were observed in an earlier study (Petrakis *et al.*, 1959).

Using autoradiography and quantitative determinations, both studies demonstrated a deposition in the lung. When uniformly labeled [^{14}C]quercetin was used, 12% of the dose of 5 mg/rat were found in the lungs 12 hr after oral administration (Petrakis *et al.*, 1959). This contrasts with the finding of less than 0.1% of 630 mg specifically labeled [4-^{14}C]quercetin/kg body wt detected in the lungs after 72 hr by Ueno *et al.* (1983). These findings indicate that a metabolite(s) of orally administered quercetin can be found in the lung, but further studies on the biokinetics are needed.

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In a perspective, tea is a low risk agent for human lung cancer when compared with smoking. In spite of large quantities of tea consumed by some segments of the population, the attributable risk is low. Its deleterious effects may thus only be manifested among those who lack protective factors or are exposed to other bronchial irritants. Studies of non-Chinese populations where personal exposure to tea is more clearly defined might provide further information on this possibility.

In summary, the aim of this study was to provide more information of the possible role of tea consumption on cancer etiology. The epidemiological data suggested that consumers of green tea had an increased risk for lung cancer. The toxicology data showed that the teas commonly drunk by the Hong Kong population contained mutagenic components. These findings support previous data and the hypothesis of an association between consumption of tea and increased risk for lung cancer. Further epidemiological studies are necessary to test this hypothesis, and the nature of the tea metabolites in the lungs need to be characterized before any final conclusions can be drawn.

REFERENCES

Ames, B. N., McCann, J., and Yamasaki, E. (1975). Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. *Mutat. Res.* 31, 347–364.

Baba, S., Furuta, T., Fujioka, M., and Goromaru, T. (1983). Studies on drug metabolism by use of isotopes XXVII: Urinary metabolites of rutin in rats and the role of intestinal microflora in the metabolism of rutin. *J. Pharm. Sci.* 72, 1155–1158.

Breslow, N. E., and Day, N. E. (1980). Statistical methods in cancer research. IARC Scientific Publication 32. IARC, Lyon, France.

Brown, J. P., and Dietrich, P. S. (1979). Mutagenicity of plant flavonols in the Salmonella/mammalian microsome test, activation of flavonol glycosides by mixed glycosides from rat cecal bacteria and other sources. *Mutat. Res.* 66, 223–240.

Brown, J. P. (1980). A review of the genetic effects of naturally occurring flavonoids, anthraquinones and related compounds. *Mutat. Res.* 75, 243–277.

Brown, S., and Griffiths, L. A. (1983). New metabolites of the naturally-occurring mutagen, quercetin, the pro-mutagen rutin and of taxifolin. *Experientia* 39, 198–200.

Cooper, J. A. D., White, D. A., and Matthay, R. A. (1986). Drug induced pulmonary disease. *Amer. Rev. Respir. Dis.* 133, 321–340.

Dean, G., Lee, P. N., Todd, G. F., and Wicken, A. J. (1977). Report on a second retrospective mortality study in North-East England. pp. 1–95. Tobacco Research Council, London, England.

Hartge, P., Hoover, R., West, D. W., and Lyon, J. L. (1983). Coffee drinking and risk of bladder cancer. *J. Natl. Cancer Inst.* 70, 1021.

Heilbrun, L. K., Nomura, A., and Stemmerman, G. N. (1986). Black tea consumption and cancer risk: A prospective study. *Br. J. Cancer* 54, 677–683.

Herrmann, K. (1976). Flavonols and flavones in food plants: A review. *J. Food Technol.* 11, 433–448.

Jensen, O. M., Wahrendorf, J., Knudsen, J. B., and Sorensen, B. L. (1986). The Copenhagen case-control study of bladder cancer. II. Effect of coffee and other beverages. *Int. J. Cancer* 37, 651–657.

Kaiser, H. E. (1967). Cancer-promoting effects of phenols in tea. *Cancer* 20, 614.

Kinlen, L. J., and McPherson, K. (1984). Pancreas cancer and coffee and tea consumption: A case-control study. *Br. J. Cancer* 49, 93.

Kinlen, L. J., Willows, A. N., Goldblatt, P., and Yudkin, J. (1988). Tea consumption and cancer. *Brit. J. Cancer* 58, 397–401.

Kirby, K. S. (1960). Induction of tumours by tannin extracts. *Br. J. Cancer* 14, 147.

2023381830

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Koo, L. C., Lee, N., and Ho, J. H.-C. (1983). Do cooking fuels pose a risk for lung cancer? A case-control study of women in Hong Kong. *Ecol. Dis.* 2, 255–265.

Koo, L. C., Ho, J. H.-C., and Saw, D. (1984). Is passive smoking an added risk factor for lung cancer in Chinese women? *J. Exp. Clin. Cancer Res.* 3, 277–283.

Koo, L. C., Ho, J. H.-C., and Lee, N. (1985). An analysis of some risk factors for lung cancer in Hong Kong. *Int. J. Cancer* 35, 149–155.

Koo, L. C., Ho, J. H.-C., Saw, D., and Ho, C. Y. (1987). Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. *Int. J. Cancer* 39, 162–169.

Koo, L. C. (1988). Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. *Nutr. Cancer* 11, 155–172.

Koo, L. C., Ho, J. H.-C., Ho, C.-Y., Matsuki, H., Shimizu, H., Mori, T., and Tominaga, S. Personal exposure to nitrogen dioxide and its association with respiratory illness in Hong Kong. *Amer. Rev. Respir. Dis.*, in press.

Korpassy, B., and Mosonyi, M. (1950). The carcinogenic activity of tannic acid. Liver tumours induced in rats by prolonged subcutaneous administration of tannic acid solutions. *Brit. J. Cancer* 4, 411.

Lubin, J. H. (1981). A computer program for the analysis of matched case-control studies. *Comp. Biomed. Res.* 14, 138–143.

Maron, D. M., and Ames, B. N. (1983). Revised methods for the Salmonella mutagenicity test. *Mutat. Res.* 113, 173–215.

McLaughlin, J. K., Blot, W. J., Mandel, J. S., Schuman, L. M., Mehl, E. S., and Fraumeni, Jr. (1983). Etiology of cancer of the renal pelvis. *J. Natl. Cancer Inst.* 71, 287.

McLaughlin, J. K., Mandel, J. S., Blot, W. J., Schuman, L. M., Mehl, E. S., and Fraumeni, Jr. (1984). A population-based case-control study of renal cell carcinoma. *J. Natl. Cancer Inst.* 72, 275.

Minocha, R., Dani, H. M., and Siddigi, M. A. (1986). Evaluation of carcinogenicity of infusions from green tea leaves by microsomal degranulation technique. *Ind. J. Exp. Biol.* 24, 224–228.

Mumford, J. L., He, X. Z., Chapman, R. S., Ao, S. R., *et al.* (1987). Lung cancer and indoor air pollution in Xuan Wei, China. *Science* 235, 217–220.

Nagao, M., Takahashi, Y., Yamanaka, H., and Sugimura, T. (1979). Mutagens in coffee and tea. *Mutat. Res.* 68, 101–106.

Nagao, M., Fujita, Y., Wakabayashi, K., Nukaya, H., Kosuge, T., and Sugimura, T. (1986). Mutagens in coffee and other beverages. *Environ. Health Perspect.* 67, 89–91.

Petrakis, P. L., Kallianos, A. G., Wender, S. H., and Shetlar, M. R. (1959). Metabolic studies of quercetin labelled with C^{14}. *Arch. Biochem. Biophys.* 85, 264–271.

Rylander, R., Haussmann, H.-J., and Tewes, F. J. (1989). Lung cancer risk by oral exposure. *In* "Present and Future of Indoor Air Quality" (C. J. Bieva, Y. Courtois, and M. Govaerts, Eds.), pp. 91–100. Elsevier Science Publishers, Amsterdam.

Stocks, P. (1970). Cancer mortality in relation to national consumption of cigarettes, soild fuel, tea and coffee. *Brit. J. Cancer* 24, 215.

Sugimura, T., Nagao, M., Kawachi, T., *et al.* (1977). Mutagen-carcinogens in food, with special reference to highly mutagenic pyrolytic products in broiled foods. *In* "Origins of Human Cancer" (H. H. Hiatt, J. D. Watson, and J. A. Winsten, Eds.), pp. 1561–1577. Cold Spring Habor Laboratory, Cold Spring Harbor, NY.

Tajima, K., and Tominaga, S. (1985). Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Japan. J. Cancer Res.* 76, 705.

Tamura, G., Gold, C., Ferro-Luzzi, A., and Ames, B. N. (1980). Fecalase: A model for activation of dietary glycosides to mutagens by intestinal flora. *Proc. Natl. Acad. Sci. USA* 77, 4961–4965.

Ueno, I., Nakano, N., and Hirono, I. (1983). Metabolic fate of [^{14}C]quercetin in the ACI rat. *J. Exp. Med.* 53, 41–50.

Uyeta, M., Taue, S., and Mazaki, M. (1981). Mutagenicity of hydrolysates of tea infusions. *Mutat. Res.* 88, 233–240.

2023381831

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Wynder, E. L., Herbert, J. R., and Kabat, G. C. (1987). Association of dietary fat and lung cancer. *J. Natl. Cancer Inst.* 79, 631–637.

Yamasaki, E., and Ames, B. N. (1977). Concentration of mutagens from urine by absorption with the nonpolar resin XAD-2: Cigarette smokers have mutagenic urine. *Proc. Natl. Acad. Sci. USA* 8, 3555–3559.

Zeiger, E., and Tennant, R. W. (1986). Mutagenesis, clastogenesis, carcinogenesis: Expectations, correlations and relations. *In* "Genetic Toxicology of Environmental Chemicals," Part B, "Genetic Effects and Applied Mutagenesis" (C. Ramel, B. Lambert, and J. Magnusson, Eds.), pp. 75–84. A. R. Liss, New York.

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DIETARY INTAKE OF CAROTENE IN NONSMOKERS WITH AND WITHOUT PASSIVE SMOKING AT HOME

STEPHEN SIDNEY, BETTE J. CAAN, AND GARY D. FRIEDMAN

There is considerable epidemiologic evidence suggesting an inverse relation between dietary intake or blood levels of beta-carotene (provitamin A) and cancer, especially lung cancer (1–6). Several studies have demonstrated that cigarette smokers have lower blood beta-carotene or carotenoid levels than nonsmokers (7–10). Therefore, beta-carotene status as measured by dietary intake or blood levels may be a confounding factor in the relation of cigarette smoking to lung cancer.

Passive smoking has been linked with an increased risk of lung cancer in nonsmokers in a number of studies (11–17). To our knowledge, there have been no studies examining the relation of beta-carotene status to passive smoking. We therefore conducted a cross-sectional study of current dietary carotene intake in a population of 2,142 nonsmokers for whom we collected information about passive smoking at home.

METHODS

Study population

The study population consisted of the 2,142 nonsmokers in the group of 3,899 Kaiser Permanente Medical Care Program members who received multiphasic health checkups in Oakland, California, during 1985 and who satisfactorily completed self-administered research questionnaires regarding tobacco use, alcohol consumption, and diet. The membership of the Kaiser Permanente Medical Care Program, which provides health care to approximately 25 per cent of the population of the San Francisco Bay Area, is heterogeneous (18). Those who take multiphasic health checkups are also heterogeneous but tend to be better educated and more health-conscious (19–20). Excluded from the study population were 766 nonsmokers who did not complete all the questions on the dietary questionnaire.

Assessment of passive smoking

Passive smoking at home was ascertained by the response to the question on the tobacco use questionnaire, "On the average, how many hours per week are you exposed to cigarette, cigar or pipe smoke in your home because of smoking by others? (Write in 000 if less than 1 hour per week) ——— hours." This questionnaire was administered to Kaiser Permanente multiphasic health checkup examinees between 1979 and 1986; a study of passive smoking based on the questionnaire has previously been published (21). Nonsmokers were classified as being exposed to passive smoke at home if the response to this question was greater than zero.

Assessment of dietary carotene intake

A 30-item semiquantitative food frequency questionnaire for the assessment of

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carotene (carotenoid precursors of vitamin A, e.g., beta-carotene, alpha-carotene, lycopene), retinol (preformed vitamin A), and total vitamin A intake was modified from a more extensive food frequency questionnaire designed by Willett et al. (22). A carotene value was assigned for an average serving size of each item, and the value was multiplied by the number of servings reported per week to obtain the weekly carotene intake. Precise estimates of specific carotenoids were not possible based on available food composition tables. The values derived from published food tables represent most of the beta-carotene plus about half the alpha-carotene and a small fraction of lycopene (10, 23).

Statistical methods

All statistical analyses were performed with SAS programs (24). *T* tests were used to assess the statistical significance of differences between means, and linear regression models were used to perform trend tests and multivariate analyses. In the multiple linear regression models, age and weight were entered as continuous variables while other characteristics were entered as indicator variables, as follows: sex; race (white, black, Hispanic, Asian, other); education (highest grade completed: 0–9, 10–12, technical/business, partial college, college graduate, post graduate, unknown); alcohol intake (nondrinker, former drinker, current drinker of less than 1, 1–2, 3–5, or 6+ drinks/day).

RESULTS

Baseline characteristics of nonsmokers exposed and those unexposed to passive smoke at home

Overall, 356 (16.6 per cent) persons of the study population reported passive smoking at home ("the exposed") (table 1). The exposed had a lower mean age and higher proportions of females, blacks, and current alcohol consumers than the unexposed. Educational status and mean body mass index were similar in the two subgroups.

TABLE 1

Baseline characteristics of nonsmokers exposed and those unexposed to passive smoke at home

Characteristic	Unexposed	Exposed
Total no.	1,786	356
Age*	42.9 ± 15.6	37.4 ± 13.7
Age range (years) (%)		
<35	36.7	49.2
35–54	36.3	37.1
≥55	27.0	13.8
Sex (% female)	59.1	68.8
Race (%)		
White	59.9	48.0
Black	18.6	33.1
All others	21.5	18.9
Education (%)		
≤High school	15.1	13.8
>High school	67.8	67.4
Unknown	17.1	18.1
Body mass index*	25.0 ± 4.8	25.9 ± 5.1
Alcohol consumption (%)		
Never and past	19.5	15.4
Current	79.8	84.3
Unknown	0.7	0.3

* Mean ± 1 standard deviation.

Dietary carotene intake in nonsmokers exposed and those unexposed to passive smoke at home

There were consistently higher mean carotene intakes in the unexposed across the sociodemographic and alcohol consumption categories examined (table 2). Most of the differences were statistically significant ($p < 0.05$). The linear regression model coefficient for passive smoking at home in relation to carotene intake (−1,185) was highly significant ($p = 0.007$), confirming the association between passive smoking at home and a lower dietary intake of carotene.

Mean dietary carotene intake by quartile of weekly duration of passive smoking at home in the exposed nonsmokers

Dietary intake of carotene was somewhat higher for the lower two than for the upper two quartiles of passive smoking duration (table 3). However, there was no statisti-

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TABLE 2

Mean dietary carotene intake (IU/day) in nonsmokers exposed and those unexposed to smoke at home, by various characteristics, and difference between means

Characteristic	Unexposed	Exposed	Difference	p^*
Total population	8,697	6,793	1,904	0.0001
Sex				
Male	8,108	6,530	1,578	0.02
Female	9,105	6,912	2,193	0.0001
Age (years)				
<35	7,374	6,144	1,230	0.03
35–54	8,786	7,035	1,751	0.009
≥55	10,370	8,458	1,912	0.10
Race				
White	8,949	6,995	1,954	0.0006
Black	8,241	6,043	2,198	0.006
All others	8,398	7,674	724	0.47
Education				
≤High school	8,682	7,158	1,524	0.22
>High school	8,680	6,900	1,780	0.0002
Unknown	8,774	6,143	2,631	0.007
Alcohol consumption				
Never and past	9,686	6,214	3,472	0.004
Current	8,429	6,917	1,512	0.005

* p value associated with the t test of the difference of the means.

TABLE 3

Mean dietary carotene intake by quartile of weekly duration of passive smoking at home in exposed nonsmokers

Quartile	Hours/week	Beta-carotene intake (IU/day)
1 (lowest)	≤2	6,718
2	3–7	8,108
3	8–24	6,032
4 (highest)	≥25	6,474

cally significant graded relation between carotene intake and duration of passive smoking either by a trend test on the unadjusted data ($p = 0.30$) or by multiple linear regression analysis of data with adjustment for age, sex, race, body weight, educational status, and alcohol intake ($p = 0.51$).

DISCUSSION

Mean dietary carotene intake was found to be lower in nonsmokers exposed to passive smoke at home than in nonsmokers who were not exposed to passive smoke at home, indicating that dietary beta-carotene intake is a potential confounder in studies of the relation between passive smoking and lung cancer. The relative risk of lung cancer associated with cigarette smoking is so great that it is unlikely to be attributable to confounding by beta-carotene intake, since the protective effects that have been associated with beta-carotene intake tend to be much lower (2, 6). However, the relative risk for lung cancer associated with passive smoking has averaged about 2 in several studies, so that evaluation of a potential confounder such as beta-carotene is important in attempting to elucidate causality (11–17). In order to assess the extent of potential confounding quantitatively, we simulated it with artificial data, assuming that a decrease in carotene intake equivalent to the difference in carotene intake between the middle of the highest and the lowest quartiles of carotene risk (approximately 2 standard deviations based on our study population) would double the risk of lung cancer. We found that an observed relative risk of 2 for passive smoking and lung cancer would be reduced to a true relative risk of approximately 1.8 with consideration of dietary carotene intake, suggesting that failure to adjust for intake of dietary carotene may inflate estimates of

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the risk of passive smoking, and its statistical significance, by amounts that are modest, yet noteworthy. Only one study of which we are aware has controlled for dietary beta-carotene intake in the analysis of the passive smoking-lung cancer relation, and this did not eliminate a positive association between passive smoking and lung cancer (17). We know of no studies that have controlled for blood levels of carotenoids in the analysis of this relation, nor do we have data regarding such blood levels in this study population.

The most likely explanation for this finding lies in important lifestyle differences between nonsmokers exposed and nonsmokers unexposed to passive smoke at home; this is supported by two differences in other characteristics. The first is the higher proportion of current alcohol consumers in the exposed subgroup, and the second is the slightly higher mean body mass index of this subgroup despite its considerably lower mean age. Although nonsmokers as a whole tend to have higher dietary intake or blood levels of carotene than cigarette smokers (7–10), it is possible that within households, the dietary preferences of nonsmokers are similar to or influenced by those of smokers, at least in regard to foods containing carotene. An alternative but, in our view, less likely hypothesis is that passive smoke exposure affects the appetite of the nonsmoker, resulting in decreased carotene intake.

We also examined dietary retinol intake. Although passive smoking at home was associated with a somewhat lower dietary retinol intake, the difference was not statistically significant ($p = 0.38$ with adjustment for age, sex, race, education, weight, and alcohol intake). The lack of a significant difference for retinol intake indicates that the intake of meat products, which are the primary dietary source of retinol, are similar in the two groups. In addition, we examined the dietary intake of carotene in relation to reported passive smoking in other settings, i.e., in small (e.g. airplane, office, car) and large (e.g. restaurant, hotel lobby, lecture hall) spaces. The results were similar to those for passive smoking at home. Nonsmokers exposed to passive smoking in small and in large spaces had lower carotene intake than nonsmokers not exposed to passive smoke in these settings ($p = 0.02$ for small spaces and 0.05 for large spaces, with the same adjustments as for passive smoking at home).

In summary, the mean dietary intake of carotene was lower in nonsmokers exposed to passive smoke at home than in nonsmokers not exposed to passive smoke at home, and the difference was statistically significant after controlling for age, sex, race, educational status, body weight, and alcohol intake by multiple linear regression. We conclude that dietary beta-carotene intake is a potential confounder and should be measured whenever possible in studies of the relation between passive smoking and lung cancer.

References

1. Shekelle RB, Lepper M, Liu S, et al. Dietary vitamin A and risk of cancer in the Western Electric Study. Lancet 1981;2:1185–9.
2. Kolonel LN, Nomura AM, Hinds MW, et al. Role of diet in cancer incidence in Hawaii. Cancer Res (Suppl) 1983;43:2397s–2402s.
3. Stahelin HB, Rosel F, Buess E, et al. Cancer, vitamins, and plasma lipids: prospective Basel study. JNCI 1984;73:1463–8.
4. Colditz GA, Branch LG, Lipnick RJ, et al. Increased green and yellow vegetable intake and lowered cancer deaths in an elderly population. Am J Clin Nutr 1985;41:32–6.
5. Menkes MS, Comstock GW, Vuilleumier JP, et al. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. N Engl J Med 1986;315:1250–4.
6. Ziegler RG, Mason TJ, Stemhagen A, et al. Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. Am J Epidemiol 1986;123:1080–93.
7. Davis C, Brittain E, Hunninghake D, et al. Relation between cigarette smoking and serum vitamin A and carotene in candidates for the Lipid Research Clinics Coronary Primary Prevention Trial. (Abstract). Am J Epidemiol 1983;118:445.
8. Witter FR, Blake DA, Baumgardner R, et al. Folate, carotene, and smoking. Am J Obstet Gynecol 1982;144:857.
9. Russell-Briefel R, Bates MW, Kuller LH. The relationship of plasma carotenoids to health and biochemical factors in middle-aged men. Am J

2023381837

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Epidemiol 1985;122:741–9.
10. Stryker WS, Kaplan LA, Stein EA, et al. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. Am J Epidemiol 1988;127:283–96.
11. Trichopoulos D, Kalandidi A, Sparros L, et al. Lung cancer and passive smoking. Int J Cancer 1981;27:1–4.
12. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 1981;282:183–5.
13. Correa P, Fontham E, Pickle LW, et al. Passive smoking and lung cancer. Lancet 1983;2:595–7.
14. Miller GH. Cancer, passive smoking and nonemployed and employed wives. West J Med 1984;140:632–5.
15. Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. JNCI 1985;75:463–9.
16. Akiba S, Kato H, Blot WJ. Passive smoking and lung cancer among Japanese women. Cancer Res 1986;46:4804–7.
17. Dalager NA, Pickle LW, Mason TJ, et al. The relation of passive smoking to lung cancer. Cancer Res 1986;46:4808–11.
18. Hiatt RA, Friedman GD. Characteristics of patients referred for treatment of end-stage renal disease in a defined population. Am J Public Health 1982;72:829–33.
19. Friedman GD, Seltzer CC, Siegelaub AB, et al. Smoking among white, black, and yellow men and women. Am J Epidemiol 1972;96:23–35.
20. Friedman GD. Effects of MHTS on patients. In: Collen MF, ed. Multiphasic health testing services. New York: John Wiley & Sons, 1978:531–49.
21. Friedman GD, Petitti DB, Bawol RD. Prevalence and correlates of passive smoking. Am J Public Health 1983;73:401–5.
22. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
23. Consumer and Food Ecomonics Institute. Composition of foods: fruits and fruit juices, raw, processed, prepared. Handbook 8–9. Washington, DC: US Department of Agriculture, 1982.
24. SAS Institute. SAS user's guide: statistics (Version 5 Edition). Cary, NC: SAS Institute, Inc, 1985.

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FACTORS THAT MIGHT CONTRIBUTE TO HIGHER SYMPTOM RATES SOMETIMES OBSERVED AROUND HAZARDOUS WASTE SITES

R Neutra, JA Lipscomb, KP Satin, D Shusterman

Symptom surveys around hazardous waste sites often show higher rates of symptoms in waste-site neighborhoods than in nearby control neighborhoods. Many processes may contribute to such results, and their role should be considered in each case. Each factor is discussed, and examples of each are presented: (1) classical toxicological response, (2) immunological or other physiogenic "dumpsite syndrome," (3) behavioral sensitization, (4) psychosomatic reaction to stress, (5) mass hysteria, (6) reporting bias, (7) confounding factors, and (8) odor as an effect modifier. It would be expensive to conduct exposure assessment and epidemiology to disentangle psychological and physical factors. A description of the desiderata of such second generation studies is provided.

CANCER AMONG FARMERS IN ICELAND

V Rafnsson, H Gunnarsdóttir

The purpose of this study was to describe the cancer pattern in a cohort of farmers in Iceland and to compare their cancer incidence to that of other Icelandic males. Special attention was given to hematological malignancy. This was a retrospective cohort study. The study population was obtained from a register at the Farmers' Pension Fund and comprised 5,922 subjects. Through date of birth and the personal identification number, the study population was linked with the Icelandic Cancer Register, which has records of cancer incidence in Iceland. The expected number of deaths were calculated using person-years of observation within 5-y age categories during respective single calendar years of the study period, multiplied by the cause-and calendar-year-specific cancer incidence rates for Icelandic men. A standardized morbidity ratio (SMR) was calculated with 95% confidence intervals.

The entire cohort shows a lower incidence for all tumors than expected. The same is true for SMRs for cancer of colon, lung, prostate, bladder and other urinary organs: 47, 41, 71, and 51, respectively. There was a significant excess incidence for Hodgkin's disease and excess for cancer of lips and skin (excluding melanomas), nervous system, and non-Hodgkin's lymphoma. There was also an excess incidence of leukemia.

The climate in Iceland is polar maritime, and grain farming is almost nonexistent. Most farmers raise either sheep or cattle or both, and haymaking occupies the farmers in the summer. It is, therefore, interesting to find similar patterns in the incidence of cancer as have been found in mortality studies of farmers who live in warmer climates.

EFFECTS OF SOCIOECONOMIC STATUS AND SMOKING ON SERUM BETA-CAROTENE

KD Waller, AH Smith

Levels of serum beta-carotene were examined in persons who lived in Wellington, New Zealand, and a gradient of lower levels of beta-carotene with lower levels of socioeconomic status was observed. This probably reflects lower dietary intake of beta-carotene in these individuals. It might also be explained by the fact that low levels of serum beta-carotene occur in cigarette smokers (independent of diet), and cigarette smoking is more common in persons of low socioeconomic status.

Socioeconomic status*	1	2	3	4	5	6
n	107	369	505	260	189	59
Mean (μg/dl)	77.2	73.5	73.9	61.9	61.0	57.1
SE (μg/dl)	4.0	1.9	2.0	1.8	2.5	3.3

*Classification system of the British Registrar General, 1–6 = high to low.

However, when this finding was examined separately for smokers and for nonsmokers and ex-smokers combined, a gradient by socioeconomic status was present for both groups. Numerous studies have suggested that increased dietary intake of beta-carotene may protect against the development of cancer of the lung, stomach, and esophagus. The incidence of lung, stomach, and esophageal cancers is increased among persons of lower socioeconomic status. Increased rates of smoking among individuals of lower socioeconomic status explain part of these differences.

The data reported herein suggest that a socioeconomic gradient exists for dietary intake of beta-carotene, independent of smoking. The gradient may also help to explain differences in cancer incidence by socioeconomic status.

Future studies of beta-carotene and cancer should be designed to consider the complex relationships between dietary beta-carotene, serum beta-carotene, cigarette smoking, socioeconomic status, and the development of cancer.

CHARACTERISTICS OF THE URINARY COTININE LEVEL IN A POPULATION OF CONTROLS FROM A CASE-CONTROL STUDY OF PEDIATRIC ASTHMA AND EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

DE Lilienfeld, R Ehrlich, M Kattan

Recent exposure to environmental tobacco smoker (ETS) was assessed in a case-control study of pediatric asthma in innercity children who were 3–14 y old. Cotinine and creatinine levels were measured in the urine of 116 nonasthmatic controls who presented to our hospital's emergency room. Analyses were undertaken of both the urinary cotinine level (UC) and the cotinine-creatinine ratio (CCR); for categorical analyses, a CCR of 30 ng/mg or greater was considered to be indicative of recent ETS exposure.

The mean cotinine level was 44.9 ng/ml, with a standard deviation of 69.3 ng/ml. The median level was 21.5 ng/ml. The skewness coefficient was 3.0. The upper quartile was among those with levels 62 ng/ml or greater; the highest decile began at 131.5 ng/ml. The maximum level observed was 360 ng/ml. The mean CCR was 47.1 ng/mg, with a standard deviation of 102.3 ng/mg. The median level was 15 ng/mg; reflecting the skewed nature of the data, the skewness coefficient was 5.3. The upper quartile began at 49 ng/mg, and the highest decile ranged from 94.3 ng/mg to 745 ng/mg.

Concerns regarding the effect of varying levels of diuresis in the population led us to focus our analysis on the CCR. The skewed nature of the distribution suggested that a log-transformation would assist in our analysis. The CCR was found to strongly correlate with the level of maternal smoking in the home ($p < .01$). No relationship was found between the CCR and sex, age, hour of day, or race. We conclude that CCR is an easily used indicator of ETS exposure.

EXPOSURE ASSESSMENT FROM OCCUPATIONAL AND NONOCCUPATIONAL SOURCES BY AN INDUSTRIAL HYGIENIST FOR BIRTH DEFECTS RESEARCH

EA Katz, GM Shaw

Occupational and other environmental exposures during pregnancy are often similar; some of these exposures may be teratogenic. In epidemiologic studies of birth defects, occupational titles have frequently been used as surrogates for exposure. To avoid the error associated with such proxy exposure measures, we have designed a process which allows an industrial hygienist who is blinded to case or control status to systematically impute exposures derived from maternal interview responses. This process allows for either separate or simultaneous assessment of maternal occupational and nonoccupational exposures. The process first requires mothers of cases and controls to recall occupational and nonoccupational tasks performed or products used around conception in response to a structured questionnaire. Maternal exposures are then determined at various a priori defined categorical levels by an industrial hygienist using a standard set of rules. One level entails a listing of 72 chemical-family groups (e.g., alcohols, ketones), to which each woman's recalled events are considered yes, no, or maybe. Several other categorical exposure levels are also pre-defined and considered, e.g., product function groups such as insecticides or combustion products. A detailed description of this approach and its exposure assessment potential, using interview data from approximately 200 women, will be presented.

TAP OR BOTTLED WATER CONSUMPTION AND SPONTANEOUS ABORTION: A 1986 CASE-CONTROL STUDY IN CALIFORNIA

GC Windham, SH Swan, L Fenster, RR Neutra

We investigated earlier findings that drinking bottled water or abstaining from tap water during pregnancy lowers the risk of spontaneous abortion (SAB). In a case-control study, approximately 2,000

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For debate: Pet birds as an independent risk factor for lung cancer

Peter A Holst, Daan Kromhout, Ronald Brand

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Abstract

To find out whether keeping birds in the home is an independent risk factor for lung cancer a case-control study was carried out in four main hospitals in The Hague, The Netherlands. Forty nine patients under 65 years of age with lung cancer each were matched for age and sex with two control subjects who attended the same general practice. Data were collected on social class, cigarette smoking, intake of β carotene and vitamin C, and alcohol consumption.

It was found that smoking, birdkeeping, and a low intake of vitamin C were significantly and independently related to the incidence of lung cancer. The odds ratio for lung cancer among people who keep birds as pets was estimated to be 6·7 after adjusting for smoking and vitamin C intake. The results of this study suggest that keeping pet birds is an independent risk factor for lung cancer.

Introduction

Smoking, occupational factors, and open air pollution do not explain fully the incidence and geographical patterns of lung cancer.[1,2] Occupational exposures to asbestos and uranium, for example, are strong risk factors. These, however, affect only a small proportion of the total population, whereas other factors such as indoor air pollution and a low intake of antioxidants in the diet—for example, β carotene—should also be considered.[3,4] Keeping birds as pets in the home contributes greatly to indoor pollution.[5]

In a survey carried out from 1972 through 1981 in a general practice in The Hague an association was found between keeping pet birds and lung cancer.[6] We decided to test the hypothesis that birdkeeping is an independent risk factor for lung cancer and report the results of a case-control study.

Methods

The study began in April 1985 in four hospitals in The Hague, which has about 450 000 inhabitants. Only patients with primary malignant neoplasms of the trachea, bronchus, and lung (International Classification of Diseases 162), who were aged under 65, had lived in The Netherlands since 1965, and were registered with one general practice in The Hague during the study were selected for the study. Patients who were too ill to fill in a questionnaire were excluded from the study. Two control subjects matched for age and sex were randomly selected in the practice for each patient. Before the study started we decided to perform an interim analysis after 1 January 1987 if the number of patients reached 50.

Between 1 April 1985 and 1 January 1987 there were 76 patients under 65 in the four hospitals with cancer of the lung. Thirteen were excluded by chest specialists, according to the protocol, because of having cerebral metastases (four) or terminal disease (nine). Thus 63 patients were eligible for entry in to the study. Fourteen of these did not participate: three were being treated by other specialists, and holiday periods and changing personnel prevented the others from participating. These 14 patients were classified as missing. The remaining 49 patients (79% of the total) participated. Two controls refused to participate and were replaced by two others selected by the same methods.

Tumours were classified according to World Health Organisation criteria by the pathologists as epidermoid carcinoma (I), small cell carcinoma (II), adenocarcinoma including bronchoalveolar carcinoma (III), and large cell carcinoma (IV).

Nine chest specialists and 48 general practitioners handed out questionnaires to patients and control subjects respectively, who completed them by themselves. The standardised questionnaire asked about occupation, smoking habits, birdkeeping, and diet. The occupation of the wage earner was taken as the indicator of the social class of the household. The participants were assigned to high and low social class according to the International Standard Classification of Occupations. Questions about smoking habits included type of tobacco, whether cigarettes, cigars, or a pipe were smoked, and amount and duration of smoking. A patient or control was considered to be a smoker if he or she had ever smoked up to and including the fifth year before cancer was diagnosed (patient) or the date of the examination (control). Information was collected on how long birds were kept and the type of birds. A patient or control was considered to be a birdkeeper if he or she had had caged birds in the home for longer than six consecutive months from five to 14 years before lung cancer was diagnosed (patient) or before the examination (control). (It takes at least five years (25-30 cell divisions) before a tumour in epithelial cells becomes detectable by x ray examination.) Information on diet was collected by questions about how often fruit and vegetables containing β carotene and vitamin C were eaten and about the consumption of alcohol. The intake of β carotene and vitamin C was calculated using average portion size and multiplying the intake of foods with their nutrient content.

Conditional logistic regression analysis was used in assessing odds ratios because of the stratified structure of the case-control study.

Results

Of the 76 patients, 29 had epidermoid carcinoma, 22 small cell carcinoma, 10 adenocarcinoma, three alveolar carcinoma, and 12 large cell carcinoma. Of the 49 patients in the study, the numbers were 14, 21, five, none, and nine. The average age of the 49 patients at diagnosis was 56·9 years. For the 37 men it was 57·9 years, and for the 12 women 53·9 years. The average

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age of the control subjects was 57. Patients and controls did not differ appreciably by social class: 78% of the patients and 67% of the controls were classified as being in the lower social class.

Of the patients, 98% were smokers, and 84% of controls were smokers. The average number of cigarette years (one cigarette year is one cigarette a day during one year) of smoking was 651 (SEM 48·0) for the patients and 448 (SEM 38·7) for the controls, a highly significant difference ($p<0·001$). The percentage of patients who kept birds was twice as high as that for controls (67% *v* 35%) (table I). It is notable that the one patient who did not smoke kept birds. Nine of the 10 patients under age 50 were birdkeepers compared with 11 of the 20 controls aged under 50. The patients had a significantly lower intake of vitamin C than the controls ($p<0·05$) (table II). No difference was observed in β carotene and alcohol intake between patients and controls.

TABLE I—*Characteristics of lung cancer patients and controls. Figures are numbers (and percentages)*

	Patients (n=49)	Controls (n=98)
Men	37 (76)	74 (76)
Women	12 (24)	24 (24)
Age (years):		
35-39	1 (2)	2 (2)
40-44	3 (6)	6 (6)
45-49	6 (12)	12 (12)
50-54	5 (10)	10 (10)
55-59	14 (29)	28 (29)
60-65	20 (41)	40 (41)
Ever smoked through 5th year before date of diagnosis:	48 (98)	82 (84)
1-15 cigarettes per day	8 (16)	29 (30)
>15 cigarettes per day	40 (82)	53 (54)
Birdkeeping five to 14 years before diagnosis:	33 (67)	34 (35)
Lower social class	38 (78)	66 (67)

TABLE II—*Details of smoking and diet for lung cancer patients and controls*

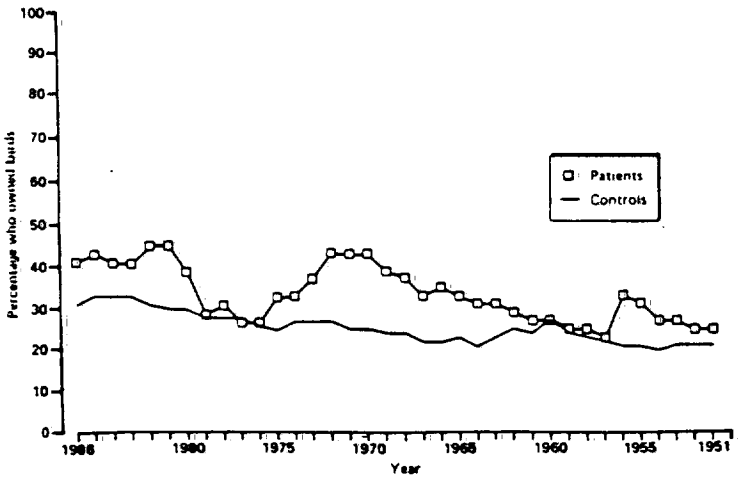
	Patients		Controls	
	Mean	SEM	Mean	SEM
Smoking (cigarette years)	651	48·0	448	38·7
Vitamin C (mg/day)	64·8	7·9	84·7	5·1
β Carotene (mg/day)	2·8	0·23	2·73	0·15
Alcohol (units per week)	12·0	1·8	10·0	1·1

Multiple conditional logistic regression analyses were carried out which show that the interactions between sex and birdkeeping and between age and birdkeeping were not significant. Thereafter the risk of lung cancer was modelled as a function of birdkeeping, smoking, vitamin C, β carotene, and alcohol intake, and social class. A backward regression analysis showed that social class and alcohol intake were not significantly related to the risk of lung cancer. Moreover, deleting these two factors from the model did not influence the coefficients of the remaining factors appreciably. Thus there was no danger of a confounding effect in simplifying the model. In the final model the risk of lung cancer was related to birdkeeping, smoking, and intake of vitamin C (table III). This analysis showed that these three risk factors were independently related to lung cancer. Birdkeepers had a risk of lung cancer 6·7 times greater than those who did not keep birds, and the adjusted odds ratios for smoking and low vitamin C intake did not differ from the crude odds ratios.

TABLE III—*Crude and adjusted odds ratios for the various risk factors of lung cancer*

	Odds ratios	
	Crude	Adjusted (95% confidence interval)
Birdkeeping (yes *v* no)	5·1	6·7 (2·2 to 20·0)
Smoking (yes *v* no)	10·0	10·0 (1·2 to 83·0)
Vitamin C intake (>50 mg/day *v* ≤50)	0·23	0·23 (0·1 to 0·6)

The figure of bird ownership from 1951 to 1986 shows that the percentage of bird keepers was always higher among the patients than among the controls and that the hobby of keeping birds increased during these years. This implies that the association that we found is not due to the chosen time interval and the definition of bird keepers.



Percentage of patients and control subjects in the study who kept birds as pets between 1951 and 1986

Discussion

The 14 patients who were eligible to participate in the study but did not do so (defined as missing) were less likely to have small cell tumours than those who participated, and their absence may have affected the relation between birdkeeping and lung cancer observed here. To assess whether there was bias an analysis was performed, assuming that in the most extreme case each missed case would have been classified as non-birdkeeper while their (fictitious) controls were randomly assigned to be a birdkeeper or a non-birdkeeper proportionally to the distribution in the other control subjects. Of course, this greatly reduced the estimated odds ratio (to 2·8), but this estimate was still significant at the 1% level. Even in this extreme case our results cannot be explained by chance alone. It is unlikely that the reason for being missed as a case is related to the exposure. Therefore the estimated odds ratio will probably not be severely biased.

People who keep birds are inhaling and expectorating excess allergens and dust particulates. Both smoking and birdkeeping cause dysfunction of lung macrophages, which is followed by local deficiency in humoral[8] and cellular immunity.[9,10] The consequence of this is less protection of the whole bronchial epithelium against continuous immunogenic and particulate material in the bronchial fluid layer.

There is also demographic evidence for an association between birdkeeping and lung cancer. There are regional differences in mortality from lung cancer in The Netherlands that cannot be explained by the differences in the age distribution of the population.[11] Unfortunately, regional information about smoking habits is not available. The rural province of North Brabant had the highest age standardised lung cancer mortality between 1969 and 1984. Most of the bird clubs and most of the organised birdkeepers are traditionally found in North Brabant. The number of

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organised bird breeders in The Netherlands has grown 10-fold since 1950. Bird breeding is pre-eminently a male hobby in our country. For years Belgium, The Netherlands, and the United Kingdom have had the highest standardised lung cancer mortality in the world.[12] Rates in the United States were always lower even though there were no fewer smokers in the past.[13]

Sixty to 80% of the trade in tropical birds is concentrated in Belgium, The Netherlands, and the UK.[14] Most of the organised birdkeepers are in these countries and most of the shows are held there. In 1980 in the United States there were 25·6 million birds in households per 230 million inhabitants and 7·5 million per 13·6 million inhabitants in The Netherlands.[15] It is possible to transport and import large numbers of birds by air cargo. Keeping species of domestic and tropical birds as pets has become very popular in this century, and this might have contributed to the increasing mortality in men from lung cancer in The Netherlands, Belgium, and the UK.

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1 Fraumeni JF Jr. Respiratory carcinogenesis. An epidemiological appraisal. *JNCI* 1975;55:1039-45.
2 Hammond EC, Garfinkel L. General air pollution in the United States. *Prev Med* 1980;9:206-11.
3 Buemaker K, de Graaf H. Air pollution indoors, a neglected variable in epidemiology? *Tijdschrift voor Sociale Gezondheid* 1967;45:74-7.
4 Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981;290:201-8.
5 Bourne WR. Birds and hazards to health. *Proceedings* 1975;215:165-71.
6 Holst PA. Bronchial carcinoma and the keeping of birds: report of a correlation observed in a general practice. *Ned Tijdschr Geneeskd* 1984;128:899-902.
7 Harrell FE Jr. The PHGLM procedure. In: *Supplemental library user's guide*. Cary, North Carolina: SAS Institute 1983:267:267-94.
8 McSharry C, Banham SW, Boyd G. Effect of cigarette smoking on the antibody response to inhaled antigens and the prevalence of extrinsic allergic alveolitis among pigeon breeders. *Clin Allergy* 1985;15:487-94.
9 Bosch FH, van Nierop MA, Meanders AE. And then the parrot appeared. *Ned Tijdschr Geneeskd* 1986;130:1465-7.
10 Daniele RP, Elias JA, Epstein PE, Rossman MD. Bronchoalveolar lavage: role in the pathogenesis and management of interstitial lung disease. *Ann Intern Med* 1985;102:93-108.
11 Hoogendoorn D. Regional differences in cancer mortality. *Ned Tijdschr Geneeskd* 1983;127:1516-25.
12 World Health Organisation. *World health statistics annual. Age-standardised death rates for selected causes*. Geneva: WHO, 1984, 1985, 1986, 1987.
13 Beese DH. *Tobacco consumption in various countries*. London: Tobacco Research Council, 1972.
14 Nilsson G. *The bird business. A study of the commercial cage bird trade*. Washington DC: Animal Welfare Institute, 1981.
15 Marks MB. Respiratory allergy to household pet birds. *Ann Allergy* 1984;52:56-7.

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Management of perinatal loss of a twin

Emanuel Lewis, Elizabeth M Bryan

Abstract

The death of a twin during pregnancy or around birth gives rise to a bewildering confusion of thoughts and feelings that can impede mourning and disturb the bereaved mother's care of a surviving twin. Every effort should be made to give the parents and siblings an experience of the dead baby. Photographs especially can reduce confusion and assist reality testing and thus facilitate the grieving process and improve the care of the surviving twin.

Introduction

Death at birth or in the womb, though natural and common events, seem contradictory and against the natural order of life. When birth and death are fused not only hurt and bitter disappointment but confusion and unreality are felt. After months of growing fullness the mother finds a sudden emptiness. Even after a live birth women may experience an emptiness, but the bereaved mother has far stronger emotions: hurt and shame, failure as a mother, and guilt without reason. She has unmanageable, conflicting feelings of love and hate for her dead baby, for other babies, and for other women in childbirth. Grievances abound and distract her from grieving. Bad feelings about what has been lost have to be disentangled from good ones to avoid idealisation on the one hand and chronic unresolved grievances on the other.[1]

A death at birth is associated with a confusion of thoughts and feelings. As a result the parents' thinking is impaired, their testing of reality is undermined, and bizarre reactions and actions can occur, not only in the bereaved family but also in those who care for them.[2] For example, a vicar reluctantly allowed a stillborn infant to be buried in his graveyard but insisted that the gravestone should be left blank.

Mourning during pregnancy is hard. For normal mourning it is necessary to hold images of the dead person in the mind until eventually there is resolution of grief and relinquishment. This process could interfere with the similar yet vitally different state of mind required during pregnancy—that of cherishing the idea of the baby inside the mother's body. The mother will feel the baby is endangered by the bad feelings and frightening ideas inevitable in the mourning process.

This same emotional complexity exists when a twin dies during pregnancy or soon after its birth.[3] When one twin survives and the other dies, not only the bereaved but also those who care for them are faced with contradictory psychological processes. The celebration of the birth of the live baby and the increasing emotional commitment of the mother contrast with the opposing processes of sorrowful relinquishment and of coming to terms with the painful emptiness of stillbirth.[4] The dead baby may seem a fantasy, particularly if no tangible memories and mementos remain. Bad memories get lost rather than relinquished. As a mother's full commitment is necessary for effective nurturing of her newborn live baby, the mourning processes may understandably be postponed; if not resumed later they may give rise to the various syndromes of failed mourning. On the other hand, the mother may grieve compulsively for the dead baby and be unable to devote herself to the care of the live baby. Excessive polarisation of feelings about the live and the dead twin may occur if she starts idealising the dead baby (her "angel baby"), especially if the surviving twin is difficult to handle or worrying because of behaviour or illness.

Management of dying and death

Every effort must be made to give the parents and siblings an experience of the dead or dying baby, as has been described for singleton stillbirth.[5,6] If one twin is likely to die the family should be encouraged to spend extra time with this one so that precious memories can be created, and the parents may later find comfort in knowing that they have given as much love and care to this baby as they could.

Twins are often premature and often surrounded by medical paraphernalia, and therefore they look

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USE OF META-ANALYSIS: EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

The statistical procedure of meta-analysis treats the results of individual studies as individual data points in an overall analysis. It has been used effectively in combining the results of randomized, controlled clinical trials of pharmaceuticals. Such studies are eminently comparable because their methodologies and study populations are very similar.

More recently, meta-analysis has been used to analyze the results of epidemiologic studies, that is, to calculate an overall relative risk as a weighted average of the relative risks of many studies. Because of the inherent differences in study design, methodology, and sample population, especially in the case of epidemiologic studies on ETS and lung cancer, questions have been raised regarding the appropriateness of using this procedure to analyze epidemiologic data. However, meta-analysis is still being used; most recently, the U.S. Environmental Protection Agency (EPA) used a meta-analysis to calculate an estimated overall relative risk for lung cancer related to exposure to environmental tobacco smoke (ETS).[1]

The EPA meta-analysis is not the first in this area. The risk estimates calculated by several other meta-analyses are given in Table 1 for comparison.[2-8]

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In addition to its meta-analysis on United States ETS-lung cancer studies, the recent paper by Fleiss and Gross (1991) presents a detailed criticism of the meta-analytical method, particularly as applied to the ETS literature.[8] This is a thorough review paper and a useful reference. Some relevant quotations follow:

> [T]he authors of the NRC report appear not to have followed the major guidelines proposed by Sacks, et al. For example, they did not provide a formal protocol for the meta-analysis, nor, apparently, did they give any consideration to the possibility of heterogeneous ORs across the several studies. (p. 134)
>
> Furthermore, the question comes to mind whether the existing epidemiological studies of a possible association between exposure to ETS and the incidence of lung cancer in non-smokers are of adequate quality. Indeed, there is the question whether any of these studies meets even minimal standards of quality. (pp. 134-135)
>
> There are many reasons for restricting attention to American studies of whether there is an elevated risk of lung cancer to non-smokers exposed to ETS relative to non-smokers not so exposed. One is that this is the population to whom policy decisions will apply and on whom those decisions should be based. (p. 135)
>
> Odds ratios from studies in other countries, on the other hand, are derived from distributions that may differ markedly from those in the U.S., and thus the ORs themselves may not be relevant to the American experience. Genetic and lifestyle differences between the U.S. population and the populations studied elsewhere (mainly in east Asia) also argue for a meta-analysis only of U.S. studies. (p. 135)

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> [U]ncritical use of meta-analysis can and does lead to unsubstantiated conclusions. Only when all the issues that we have discussed are considered and possibly accounted for is it possible to apply meta-analysis so that the overall result is scientifically valid. (p. 137)
>
> It is very unlikely that the biases present in the epidemiological studies of the possible association between exposure to ETS and the risk of lung cancer can ever be removed. The meta-analysis performed by the NRC must either be completely discounted or, as Stein concluded so succinctly in another context, considered a mere 'computational exercise.' (p. 137)

(An editorial comment on this paper by Spitzer is also included.[9])

Copies of some of the referenced articles are included at Tabs 1-4. They are highlighted in yellow for useful information, and in blue for adverse information.

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Table 1. Results of Meta-Analyses of Epidemiologic Studies of Spousal Smoking and Female Lung Cancer

Meta-Analysis	Summary Risk Estimate	Studies Included
Wald, et al., 1986	1.35 (95% CI 1.19-1.54)	13; 10 case-control, 3 cohort
NRC, 1986	1.32 (95% CI 1.16-1.51)	13; 10 case-control, 3 cohort
Blot and Fraumeni, 1986	1.3 (95% CI 1.1-1.5)	12; 10 case-control, 2 cohort
Wells, 1988	1.44 (95% CI 1.26-1.66)	17; 14 case-control, 3 cohort
EPA, 1990	1.41 (95% CI 1.26-1.57)	22; 19 case-control, 3 cohort
	1.25 (95% CI 1.03-1.52)	8 U.S. studies; 7 case-control, 1 cohort
Letzel and Überla, 1990	1.118 1.076	12; 10 case-control, 2 cohort 11; 9 case-control (Trichopoulos excluded), 2 cohort
Fleiss and Gross, 1991	1.12 (95% CI 0.95-1.30)	9 U.S. studies; 8 case-control, 1 cohort
Layard and LeVois, 1991 (unpublished)	1.08 (95% CI 0.96-1.22)	26; 23 case-control, 3 cohort

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REFERENCES

1. United States Environmental Protection Agency, "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," (Review Draft) EPA/600/6-90/006A, May, 1990.

2. Wald, N.J., Nanchahal, K., Thompson, S.G. and Cuckle, H.S., "Does Breathing Other People's Tobacco Smoke Cause Lung Cancer?," British Medical Journal 293: 1217-1222, 1986.

3. National Research Council, Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects (Washington: National Academy Press, 1986).

4. Blot, W.J. and Fraumeni, J.F., "Passive Smoking and Lung Cancer," Journal of the National Cancer Institute 77(5): 993-1000, 1986.

5. Wells, A.J., "An Estimate of Adult Mortality in the United States from Passive Smoking," Environment International 14: 249-265, 1988.

6. Letzel, H. and Überla, K., "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.

7. Layard, M.W. and LeVois, M.E., Letter to Dr. Donald G. Barnes, Director of the Science Advisory Board, United States Environmental Protection Agency, April 9, 1991.

8. Fleiss, J.L. and Gross, A.J., "Meta-Analysis in Epidemiology, with Special Reference to Studies of the Association Between Exposure to Environmental Tobacco Smoke and Lung Cancer: A Critique," Journal of Clinical Epidemiology 44(2): 127-139, 1991.

9. Spitzer, W.O., "Meta-Meta-Analysis: Unanswered Questions About Aggregating Data," Journal of Clinical Epidemiology 44(2): 103-107, 1991.

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MEDICAL PRACTICE

Contemporary Themes

Does breathing other people's tobacco smoke cause lung cancer?

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Abstract

The available epidemiological studies of lung cancer and exposure to other people's tobacco smoke, in which exposure was assessed by whether or not a person classified as a non-smoker lived with a smoker, were identified and the results combined. There were 10 case-control studies and three prospective studies. **Overall, there was a highly significant 35% increase in the risk of lung cancer among non-smokers living with smokers compared with non-smokers living with non-smokers (relative risk 1·35, 95% confidence interval 1·19 to 1·54).** Part of this increase was almost certainly caused by the misclassification of some smokers as non-smokers. As smokers, who are more likely to get lung cancer than non-smokers, tend to live with smokers this misclassification probably exaggerated the estimated increase in risk. Adjustment for this error reduced the estimate to 30% (relative risk 1·30), but as people who live with non-smokers may still be exposed to other people's smoke this estimate was revised again to allow for the fact that a truly unexposed reference group was not used. **The increase in risk among non-smokers living with smokers compared with a completely unexposed group was thus estimated as 53% (relative risk of 1·53).**

This analysis, and the fact that non-smokers breathe environmental tobacco smoke, which contains carcinogens, into their lungs and that the generally accepted view is that there is no safe threshold for the effect of carcinogens, leads to the conclusion that breathing other people's tobacco smoke is a cause of lung cancer. About a third of the cases of lung cancer in non-smokers who live with smokers, and about a quarter of the cases in non-smokers in general, may be attributed to such exposure.

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Introduction

It has been shown that non-smokers who live with smokers are generally more exposed to other people's tobacco smoke, and that their exposure is greater both inside and outside the home, than non-smokers living with non-smokers.[1] The epidemiological studies that have compared the risk of lung cancer in these two groups of non-smokers therefore provide a valid means of assessing the effect of exposure to environmental tobacco smoke ("passive smoking").[2-14] Few of the studies have shown a significant risk of lung cancer associated with exposure to such smoke, but this cannot be taken as negative evidence because most of the studies were too small to detect the small excess risk that would be expected. To overcome this problem we present here an analysis that combines the results from all 13 studies. We have also interpreted the collective evidence and judged whether there is a causal association between exposure to environmental tobacco smoke and lung cancer.

Methods

We reviewed the available epidemiological studies of lung cancer and exposure to environmental tobacco smoke, in which exposure was assessed by whether the subject lived with a smoker (generally taken as having a spouse who was a smoker). In the case-control studies the frequency of living with a smoker was compared in reported lifelong non-smokers with and without lung cancer. In the prospective studies the incidence of lung cancer was compared in reported lifelong non-smokers who lived with a smoker and in those who did not. Three studies were excluded, two because insufficient data on non-smokers were available[3,14] and the other because it used population estimates of smoking prevalence for comparison rather than an explicit control group.[17] Of the two reports by Koo *et al* on the same group of subjects, the most recent one has been used for this analysis.[9,10] We thus analysed the 10 remaining case-control studies[4-13] and three prospective

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studies[12-14] (see table I). In these studies most of the cases of lung cancer were in women (990/1125).

Of the 10 case-control studies, six used hospital controls with diseases that were not related to smoking[2-4 6 7 9] and four used population based controls.[5 8 10 11] The controls in all the studies except one were age matched to individual subjects; in the exception the mean ages of cases and controls were similar.[4] Controls were matched by sex and usually by hospital or geographical area.

Subjects had been ascertained to be non-smokers by interviews of either the subject or the subject's next of kin (usually with a structured questionnaire) except in two studies, which used postal questionnaires alone.[11 12] Categorisation of the smoking habits of the person living with the subject differed somewhat between studies. Usually all ex-smokers and current smokers were amalgamated into one smoking category. In studies—for example, that of Trichopolous *et al*[4]—where an ex-smoking category was separately defined these data were excluded from our analysis. Most studies excluded unmarried subjects or those living alone, but in a few studies these groups were amalgamated with the category of subjects living with a non-smoker.

Some of the case-control studies obtained relative risk estimates after adjustment for certain factors such as occupation and type of housing. These estimates were virtually identical to those that were unadjusted, indicating that the factors considered were not important. In some studies matched analyses were performed, but again this had no material effect. The published estimates were always close to those calculated in this paper for inclusion in our pooled analysis. In the prospective studies adjustment for age was important, and we therefore used the age adjusted relative risk estimates published by the authors.

The risks of lung cancer of exposed and unexposed subjects are compared here only within each study, and the differences in risk within each study are then combined over all the studies. This avoids directly comparing data from one study with those of another. Details of the statistical analysis are given in the Appendix. In summary, relative risk estimates from each study were combined across studies using published methods.[19 20] The method gives a weighting to each of the studies according to the precision of its estimate of risk. For the individual and pooled relative risk estimates 95% confidence limits were derived from calculations on a log scale as ln (relative risk) ± (2SE (ln (relative risk))).

Results

Table I shows the relative risk estimates of lung cancer associated with exposure to environmental tobacco smoke in the 13 epidemiological studies and the summary estimate based on all the studies combined. Figure 1 shows relative risks and 95% confidence intervals.

The summary estimate of the increased risk of lung cancer in non-smokers who lived with smokers compared with that in non-smokers who lived with non-smokers was 35% (relative risk 1·35). The 95% confidence limits of this estimate (1·19 to 1·54) indicate that the result is unlikely to have arisen by chance (p<0·0001). The estimate of increased risk from the prospective studies was similar to the estimate from the case-control studies (table I). No relative risk from any one study was inconsistent with the summary relative risk estimate. A formal test for heterogeneity[21] was not significant (χ^2_{13} = 20·0, p>0·2).

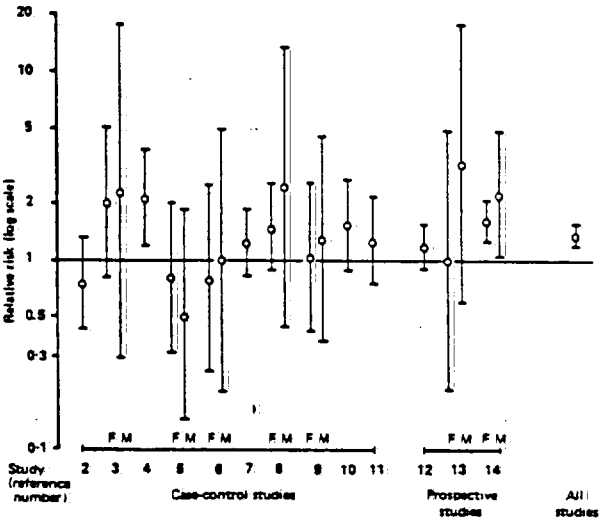

FIG 1—The relative risk of lung cancer (estimate and 95% confidence interval) in non-smokers who live with smokers compared with non-smokers who live with non-smokers for each of the studies given in table I and the summary estimate based on all the studies combined. The estimate for females is shown first for studies based on both male and female subjects.

TABLE I—*Summary of the epidemiological studies of risk of lung cancer in non-smokers associated with exposure to environmental tobacco smoke*

Authors	Study location	Sex	Exposed to environmental smoke: Lung cancer	Exposed to environmental smoke: No lung cancer	Unexposed to environmental smoke: Lung cancer	Unexposed to environmental smoke: No lung cancer	Relative risk*	95% Confidence limits	
				Case-control studies					
Chan and Fung[2]	Hong Kong	F	34	66	50	73	0·75	0·43	1·31
Correa *et al*[3]	US	F	14	61	8	72	2·03	0·81	5·08
		M	2	26	6	154	2·29	0·30	17·33
Trichopoulos *et al*[4]	Greece	F	38	81	24	109	2·11	1·17	3·78
Buffler *et al*[5]	US	F	33	164	8	32	0·80	0·32	1·99
		M	5	56	6	34	0·50	0·14	1·83
Kabat and Wynder[6]	US	F	13	15	11	10	0·79	0·25	2·48
		M	5	5	7	7	1·00	0·20	5·06
Garfinkel *et al*[7]	US	F	91	254	43	148	1·23	0·81	1·86
Akiba *et al*[8]	Japan	F	73	188	21	82	1·48	0·87	2·52
		M	3	9	16	101	2·45	0·45	13·45
Lee *et al*[9]	England	F	22	45	10	21	1·03	0·41	2·58
		M	8	14	7	16	1·30	0·37	4·54
Koo *et al*[10]	Hong Kong	F	51	66	35	70	1·54	0·89	2·67
Pershagen *et al*[11]†	Sweden	F	33	150	34	197	1·27	0·75	2·18
Values overall for case-control studies			425		286		1·27	1·05	1·53
				Prospective studies					
Garfinkel[12]‡	US	F	88	127 164	65	49 422	1·18	0·90	1·54
Gillis *et al*[13]	Scotland	F	6	1 388	2	521	1·00	0·20	4·91
		M	4	306	2	515	3·25	0·60	17·65
Hirayama *et al*[14]	Japan	F	146	63 287	37	21 858	1·63	1·25	2·11
		M	7	1 003	57	19 222	2·25	1·04	4·86
Values overall for prospective studies			251		163		1·44	1·20	1·72
Values overall for all studies			676		449		1·35	1·19	1·54

*The method used to calculate the relative risk for the case-control studies and the prospective studies is given in the Appendix.
†Data shown obtained as a personal communication.
‡The number of women not exposed to environmental tobacco smoke was quoted as 28% of 176 739.[12]

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Discussion

Our analysis of the epidemiological studies taken together showed an increased risk of lung cancer in non-smokers living with smokers compared with non-smokers living with non-smokers, a result that is unlikely to have arisen by chance. This result must represent either a direct and causal effect of exposure to environmental tobacco smoke or be partly or completely due to bias.

A potentially serious source of bias arises from the probability that some current smokers and ex-smokers will report themselves or be reported by others as never having smoked. **They are more likely to develop lung cancer than those correctly classified as lifelong non-smokers** and they are also more likely to live with a smoker as couples tend to share the same smoking habits. People reported to be lifelong non-smokers who live with smokers will therefore seem to have an increased risk of lung cancer. In order to quantify the extent to which this misclassification bias could have accounted for the risk found in the epidemiological studies it is necessary to estimate four parameters: the proportion of current and ex-smokers misclassified in this way, the risk of lung cancer in those who are misclassified, the extent to which smokers live with smokers—that is, aggregate together, and the proportion of men and women who have smoked at some time.

PROPORTION OF EVER SMOKERS WHO ARE REPORTED AS NON-SMOKERS

The proportion of people who say that they have never smoked but are, in fact, likely to be current smokers may be estimated by using the data from studies in which the distributions of nicotine and its metabolite, cotinine, were measured in those who described themselves as non-smokers. Both nicotine and cotinine are derived virtually exclusively from tobacco. Table II summarises the results of four such studies, in which data on smokers were also given.[22-24]

TABLE II—*Cotinine and nicotine concentrations in non-smokers as markers of misclassification*

Study	Marker	No of reported non-smokers	No of reported smokers	No (%) of non-smokers with marker concentration >10% of smokers' concentration*
Feyerabend *et al*[22]	Urinary nicotine	56	82	0
Wald *et al*[23]	Urinary cotinine	221	131	2 (0·9)†
Pojer *et al*[24]	Plasma cotinine	181	187	6 (3·3)‡
Haddow *et al*[‖]	Serum cotinine	232	305	3 (1·3)§
Total		690	705	11 (1·6)

*Smokers' median concentration (mean concentration in the study of Feyerabend *et al*).
†19% and 24% of smokers' concentration.
‡Three 10-14%, one 15-29%, two 30-44% of smokers' concentration (individual values not specified).
§14%, 16%, and 68% of smokers' concentration.
‖Personal communication.

In all, there were 690 people who described themselves as non-smokers, 11 of whom (1·6%) had concentrations of nicotine or cotinine greater than a tenth of the median concentration (or, in one study, the mean) found in smokers, though these 11 had still on average only about a quarter of that median concentration in smokers. If, as is the case for women in Britain, about 50% are reported never to have smoked,[25] 35% to be current smokers, and 15% to be ex-smokers then 2·1% of ever smokers (1·6%×(50%+15%)/(35%+15%)) may be current smokers who are not classified as such.

The proportion of ever-smokers who, though ex-smokers, are reported never to have been smokers was estimated in the Medical Research Council national survey of health and development (N Britten, personal communication). In this study information on smoking was collected on several occasions from 3274 of the subjects from the survey. Of all the subjects who had previously reported that they smoked, 4·9% said in their most recent interview that they had never smoked as much as one cigarette a day. Nearly all of these people (93%) had reported smoking 10 or more years earlier but not more recently, and, on average, they had smoked only about a third as many cigarettes per day as those who reported that they were current smokers and had also reported smoking previously.

From these two sources the proportion of ever smokers who are misclassified as lifelong non-smokers seems to be about 7% (2·1%+4·9%).

RELATIVE RISK OF LUNG CANCER IN CURRENT AND EX-SMOKERS MISCLASSIFIED AS NON-SMOKERS

In the epidemiological studies considered in this paper nearly 90% of the cases of lung cancer occurred in women. The study by Hammond showed that women aged 35-74 years who smoked 20 or more cigarettes a day had a 4·9 fold increased risk of lung cancer compared with non-smokers[26]; the study by Doll *et al* yielded an estimate of 6·4 for women smoking 15-24 cigarettes daily.[27] Both studies were conducted a number of years ago, and with the increased duration of smoking in women in recent years current estimates of the relative risk would be closer to about 8. The risk will, however, be much less in both current and ex-smokers who report incorrectly that they are lifelong non-smokers. Such current smokers smoked, on average, only about a quarter as much as other current smokers and might be expected to have an excess risk of lung cancer a quarter as much—that is, an approximate threefold risk of lung cancer [1+¼(8−1)]. Ex-smokers who had, in general, given up at least 10 years ago, and therefore had about a quarter of the excess relative risk of continuing smokers[28] and smoked only a third as much as continuing smokers, will have an even lower risk, say about 1·5 [1+¼×⅓(8−1)]. The average of 3 and 1·5 weighted according to the relative proportion of current and ex-smokers in those misclassified yields a two fold risk.

AGGREGATION OF SMOKERS

The extent to which smokers live with other smokers can be expressed numerically as the odds ratio in a 2×2 table categorising the smoking state of the subject by the smoking state of those with whom the subject lives. We call this ratio the aggregation factor. It was estimated to be 3·94 based on interviews with 364 subjects (table III), 2·22 based on a study of 4064 subjects,[19] 3·55 for men and 3·07 for women based on a study of 8800 subjects (P N Lee, unpublished findings). We have adopted a figure of 3·0.

PROPORTION OF MEN AND WOMEN WHO HAVE SMOKED AT SOME TIME

The proportions of men and women in the population who have smoked at some time influences the extent of the misclassification bias; the greater the proportions (of women in particular), the greater the bias. We chose quite high proportions in the calculations

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TABLE III—*Number of smokers and non-smokers* related to smoking habits of their spouses and the odds ratio indicating the extent of aggregation†*

Spouse	Subject		Total
	Ever smoker	Lifelong non-smoker	
Ever smoker	84	13	97
Lifelong non-smoker	164	100	264
Total	248	113	361

*Based on interviews of 200 women and 164 men attending a health screening centre in London or working in the civil service in Newcastle in 1985, excluding three people who lived alone.
†Aggregation factor = 3·94.

—namely, 50% of women and 70% of men—representative of the higher figures in the countries in which the studies on exposure to environmental tobacco smoke were carried out as this tends to overestimate rather than underestimate the effect of the bias.

Figure 2 shows how, on the basis of these four estimates, the relative risk of lung cancer in association with exposure to environmental tobacco smoke of 1·35 (the overall estimate from table I) would be observed if the true relative risk for non-smokers exposed to such smoke was 1·30. Under these conditions the 95% confidence limits of 1·19 to 1·54 for the observed relative risk of 1·35 correspond to limits of 1·14 to 1·50 for the estimated true relative risk of 1·30. The misclassification bias is therefore unlikely to account for all the association between lung cancer and exposure to this type of smoke.

Table IV illustrates the effect of adopting different estimates of the variables that affect the misclassification bias by showing the proportion of ever smokers who would need to be misclassified as lifelong non-smokers to account for observed relative risks from 1·4 to 1·1. In particular, table IV may be used to determine how large these estimates would have to be to account completely for the observed increase in risk. Lee has produced a similar illustration of the bias[9] but believes (unpublished findings) that its effect is greater than we do, mainly because he assumed a higher rate of misclassification (more than 12% of those who reported themselves to be non-smokers) and applied to misclassified smokers what we consider to be too high a risk of lung cancer—in particular, a 10 fold relative risk in the 1·4% of misclassified current smokers.

The possibility of a dose response relation between exposure to

TABLE IV—*Proportion (%) of ever smokers misclassified as lifelong non-smokers that would be needed to convert specified observed relative risks of lung cancer associated with exposure to environmental tobacco smoke to unity according to the extent of smoker aggregation and the relative risk of lung cancer in ever smokers misclassified as non-smokers*

Observed relative risk of lung cancer in studies of exposure to environmental tobacco smoke	Aggregation factor	Relative risk of lung cancer in those misclassified as lifelong non-smokers		
		2	4	8
1·4	2	*	*	*
	3	*	36·0	9·5
	4	*	20·0	6·8
1·3	2	*	*	14·0
	3	*	18·0	6·3
	4	*	13·0	4·7
1·2	2	*	20·0	6·7
	3	73	9·7	3·8
	4	34	7·4	3·0
1·1	2	31	6·9	2·8
	3	15	4·2	1·7
	4	11	3·3	1·4

*Even 100% misclassification would not give the observed relative risk.

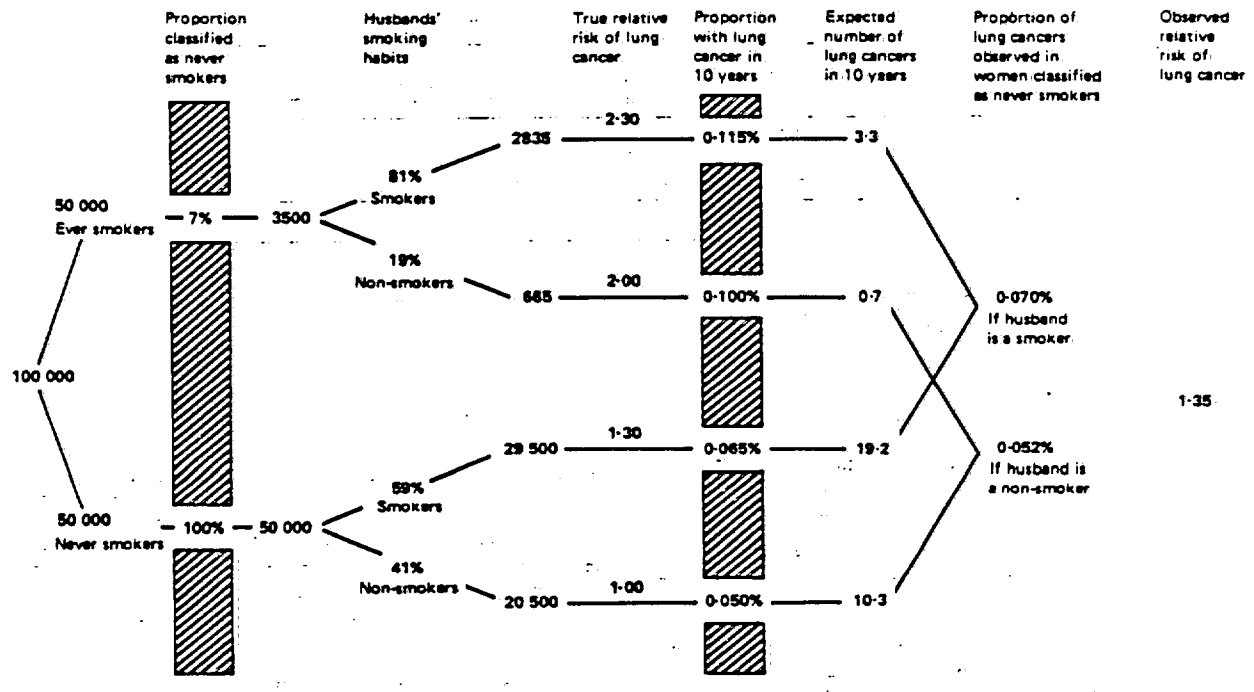

FIG 2—Illustration of how the misclassification bias transforms a true relative risk of lung cancer of 1·30 to an observed relative risk of 1·35 in non-smoking women, comparing those married to smokers with those married to non-smokers assuming that: (*a*) the proportion of current and ex-smokers misclassified as non-smokers is 7%; (*b*) the true relative risk of lung cancer among women misclassified as non-smokers is 2·0 for those married to non-smokers and 2·30 for those married to smokers; (*c*) the aggregation factor of smoking state within marriages is 3·0 (see text and table III); and (*d*) the proportion of ever smokers is 50% for women and 70% for men, which, with an aggregation factor of 3, determines the estimates of a husband's smoking habits according to the woman's smoking; 3 = (81% × 41%)/(19% × 59%). (The lung cancer incidence of 0·050% per 10 years in non-smoking women was chosen for illustration but does not affect the conclusion.)

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environmental tobacco smoke (assessed by the amount and duration of a partner's smoking) and lung cancer was investigated in eight of the epidemiological studies[1,4,7,8,10-13] and identified in five.[1,4,7,8,11] This supports a causal explanation, but the evidence is weak. It could also be explained by bias if smokers, some of whom had been misclassified as non-smokers, had a cigarette consumption (and therefore a lung cancer risk) that was correlated with the cigarette consumption of the person with whom they lived.

Other potential sources of bias are unlikely to have distorted the estimate of risk. In the case-control studies cases may have denied smoking more than controls or their interviewers may have investigated their non-smoking status to a different extent. There is no evidence to suggest this, and indeed the prospective studies which by design avoided this bias yielded similar results to the case-control studies. Positive studies may have been more likely to have been published than negative ones. We are, however, unaware of unpublished negative studies, and once the initial positive studies had been reported the incentive to publish negative studies was at least as great as that to publish positive ones. We conclude, therefore, that at least part of the association is causal, and our best estimate is that the excess risk of lung cancer due to exposure to environmental tobacco smoke, as judged by the difference in exposure in those who do and those who do not live with smokers, is about 30% (relative risk 1·30).

This figure is an underestimate of the true risk of exposure to environmental tobacco smoke typical of those who live with smokers because some of the non-smokers who live with non-smokers and who are not exposed to such ambient smoke at home are exposed to it in other settings—for example, at work. The relative risk estimate of 1·30 is therefore based on a reference group that is partially exposed. This can be allowed for to some extent by the use of data on urinary cotinine concentrations in non-smokers living with smoking or non-smoking partners. In the study by Wald and Ritchie the average urinary cotinine concentration among non-smokers married to smokers was about three times that among non-smokers married to non-smokers.[1] If y is the excess lung cancer risk in non-smokers living with non-smokers then, assuming a linear relation between the excess risk in non-smokers and the extent of exposure, the excess lung cancer risk in non-smokers living with smokers is 3y and the relative risk of 1·30 above must satisfy the equation $1{\cdot}30=(1+3y)/(1+y)$. When the equation is solved $y=0{\cdot}176$, and the excess risk in non-smokers living with smokers may be estimated as 53% ($3y\times100\%$) and in non-smokers living with non-smokers as 18% ($y\times100\%$). This estimate of increased risk would indicate that about a third of cases of lung cancer in non-smokers living with smokers, and about a quarter of cases in non-smokers in general, may be attributed to exposure to environmental tobacco smoke. (The excess risk divided by the total risk for non-smokers living with non-smokers is 0·53/1·53, or about a third, and for non-smokers in general is 0·38/1·38, or about a quarter; 0·38 is an average of the excess risks of 0·53 and 0·18 weighted according to the estimated proportions of spouses who had smoked at some time.)

The effect of exposure to such smoke on lung cancer may be estimated from data on biological markers in smokers. We have avoided performing a detailed analysis of this kind as it entails several assumptions that with present knowledge are difficult to support—for example, as to the quantitative relation between nicotine in ambient smoke and in mainstream smoke and the relation of these values to the concentration of the carcinogens in tobacco smoke. It is, however, pertinent that in non-smokers who live with a smoker urinary cotinine concentrations are about 1% of those found in active smokers.[12,28] In the study that examined urinary cotinine concentrations in cigarette smokers and in non-smokers classified according to whether or not they lived with smokers, further analysis showed that the mean concentrations were in the ratio 200:3:1, respectively. This ratio is broadly in line with the excess risk of lung cancer in the three groups—namely, 13, 0·3, and 0, respectively, suggesting that the observed risk is reasonably consistent with what might be expected. (We used the figure of 13 here, instead of 7, as it relates to men,[28] and (*a*) in the cotinine study all the smokers were men and (*b*) in women living with a smoker the number of years of exposure is likely to be closer to the number of years of smoking among men than among women.)

We conclude that breathing other people's tobacco smoke does cause lung cancer, and our conclusion rests on several observations. Firstly, carcinogens in tobacco smoke are released into the air. Secondly, tobacco smoke is breathed into the lungs by non-smokers. Thirdly, the general view is that exposure to carcinogens does not have a threshold below which there is no effect. Fourthly, people known to have an increased exposure to environmental tobacco smoke seem to have an excess risk of lung cancer, which is not explained satisfactorily by bias. Fifthly, the magnitude of the excess seems reasonable in view of the extent of exposure, and, sixthly, there is a dose response relation between the extent of exposure and risk. In view of all these observations, we could not have concluded otherwise.

This paper was produced while one of the authors (NJW) was a member of the National Academy of Science Committee on Passive Smoking (Chairman Barbara Hulka), which has produced a report, *Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects*, to be published shortly by the National Academy. We would like to thank members of that committee, particularly James Robins, and Diane Wagener and Marvin Schneidermann on the secretariat of the committee, for their constructive criticism and help in developing the ideas expressed in this paper. We also thank Jane Stock for collection of data, Nicky Britten, Linda Koo, and Goran Pershagen for allowing us to use their unpublished data, Malcolm Law for his comments, and the Cancer Research Campaign and the British United Provident Association for their financial support.

References

1 Wald NJ, Ritchie C. Validation of studies on lung cancer in non-smokers married to smokers. *Lancet* 1984;ii:1067.
2 Chan WC, Fung SC. Lung cancer in non-smokers in Hong Kong. Cancer Campaign. In: Grundmann E, ed. *Cancer epidemiology*. Vol 6. New York: Gustav Fischer Verlag, 1982: 199-202.
3 Correa P, Pickle LW, Fontham E, Lin Y, Haenszel W. Passive smoking and lung cancer. *Lancet* 1983;ii:595-7.
4 Trichopoulos D, Kalandidi A, Sparros L. Lung cancer and passive smoking: conclusion of Greek study. *Lancet* 1983;ii:667-8.
5 Buffler PA, Pickle LW, Mason TJ, Contant C. The causes of lung cancer in Texas. In: Mizell M, Correa P, eds. *Lung cancer: causes and prevention*. New York: Verlag Chemie International, 1984:83-99.
6 Kabat GC, Wynder EL. Lung cancer in nonsmokers. *Cancer* 1984;53:1214-21.
7 Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. *Journal of the National Cancer Institute* 1985;75:463-9.
8 Akiba S, Kato H, Blot WJ. Passive smoking and lung cancer among Japanese women. *Cancer Res* 1986;46:4804-7.
9 Lee PN, Chamberlain J, Alderson MR. Relationship of passive smoking to the risk of lung cancer and other smoking-associated diseases. *Br J Cancer* 1986;54:97-105.
10 Koo LC, Ho JH-C, Fraumeni JF, Blot WJ, Lubin JH, Stone BJ. Measurements of passive smoking and estimates of risk for lung cancer among non-smoking Chinese females. *International Journal of Cancer* (in press).
11 Pershagen G, Hrubec Z, Svensson C. Passive smoking and lung cancer in Swedish women. *Am J Epidemiol* (in press).
12 Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *Journal of the National Cancer Institute* 1981;66:1061-6.
13 Gillis CR, Hole DJ, Hawthorne VM, Boyle P. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur J Respir Dis [Suppl]* 1984;133:121-6.
14 Hirayama T. Cancer mortality in nonsmoking women with smoking husbands in a large-scale cohort study in Japan. *Prev Med* 1984;13:680-90.
15 Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 1985;121:37-48.
16 Wu AH, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. *Journal of the National Cancer Institute* 1985;74:747-51.
17 Knoth A, Bolte H, Schmidt F. Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen. *Medizinische Klinik* 1983;78:54-9.
18 Koo LC, Ho JH, Lee N. An analysis of some risk factors for lung cancer in Hong Kong. *Int J Cancer* 1985;35:149-55.
19 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-71.
20 Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiological research: principles and quantitative methods*. New York: Van Nostrand Rheinhold, 1982:341-2.
21 Woolf B. On estimating the relation between blood group and disease. *Ann Hum Genet* 1955;19:251-3.
22 Feyerabend C, Higenbottam T, Russell MAH. Nicotine concentrations in urine and saliva of smokers and non-smokers. *Br Med J* 1982;284:1002-4.
23 Wald NJ, Boreham J, Bailey A, Ritchie C, Haddow JE, Knight G. Urinary cotinine as a marker of breathing other people's tobacco smoke. *Lancet* 1984;i:230-1.
24 Power R, Whitfield JB, Poulous V, Eckhard JF, Richmond R, Hensley WJ. Carboxyhemoglobin, cotinine, and thiocyanate assay compared for distinguishing smokers from non-smokers. *Clin Chem* 1984;30:1377-80.
25 Office of Population Censuses and Surveys. *General household survey 1982*. London: HMSO, 1984.
26 Hammond EC. Smoking in relation to the death rate of one million men and women. *National Cancer Institute Monographs* 1966;19:127-204.
27 Doll R, Gray R, Hafner B, Peto R. Mortality in relation to smoking: 22 years' observations on female British doctors. *Br Med J* 1980;280:967-71.
28 Doll R. Practical steps towards the prevention of bronchial carcinoma. *Scot Med J* 1970;15:433-47.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

29 Lehnert G, Garfinkel L, Hirayama T, *et al*. Round table discussion from symposium on medical perspectives on passive smoking (Vienna, April 1984). *Prev Med* 1984;13:732-3.
30 Russell MAH, Jarvis MJ, West RJ. Use of urinary nicotine concentrations to estimate exposure and mortality from passive smoking in non-smokers. *British Journal of Addiction* 1986;81: 275-81.
31 Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J* 1976;ii:1525-30.

(Accepted 30 October 1986)

Appendix

Let the number of subjects in each of the epidemiological studies be classified by disease status and exposure in this way:

	With lung cancer	Without lung cancer	Total
Living with a smoker	a	b	m_1
Living with a non-smoker	c	d	m_2
Total	m_3	m_4	T

The relative risk of lung cancer in association with living with a smoker (and its confidence limits) were then calculated as follows:

For each of the case-control studies—In the absence of a risk from exposure to environmental tobacco smoke the expected number of people (E) who live with a smoker and have lung cancer is m_1m_3/T. The difference (O−E) between observed (O) and expected (E) numbers of people with lung cancer who live with a smoker was calculated, the variance of this difference being

$$\mathrm{Var}(O-E)=\frac{m_1\times m_2\times m_3\times m_4}{T\times T\times(T-1)}.$$

The natural logarithm of the relative risk (RR) was estimated for each study using[19]

$$\ln RR=\frac{O-E}{\mathrm{Var}(O-E)}.$$

Confidence limits for ln RR were calculated using the variance

$$\mathrm{Var}(\ln RR)=1/\mathrm{Var}(O-E)$$

and the estimate of RR and its confidence limits were estimated from the calculations on a logarithmic scale by exponentiation.

For each of the prospective studies—For prospective studies the published relative risk values were used in the following calculations as in all of the articles the authors had estimated the relative risk, adjusting for variables such as age. For those studies in which relative risk estimates were given separately for different levels of smoking by the spouse[12 14] a combined estimate of relative risk was calculated as an average of the individual estimates, each weighted inversely proportional to its variance. (See method below for combining the prospective studies.) The variance of the natural logarithm of the relative risk was derived from the published confidence limits for the estimate of relative risk in all studies except one[13] (where adjustment for age seemed of little importance and no confidence limits had been published), in which the method given above for the case-control studies was used.

For combining the results from the studies—The method used for combining the results from the case-control studies is based on that of Yusuf *et al*.[19] The overall estimate of RR was calculated by adding the values of (O−E) and their variances for all the studies and using

$$\ln RR=\frac{\Sigma(O-E)}{\Sigma\mathrm{Var}(O-E)}$$

and for the variance

$$\mathrm{Var}(\ln RR)=\frac{1}{\Sigma\mathrm{Var}(O-E)}$$

The method used for combining the results from the prospective studies is based on a pooled value for the ln RR calculated as an average of the individual ln RRs, each inversely weighted according to its variance.[28]

$$\ln RR=\sum\frac{(\ln RR)}{\mathrm{Var}(\ln RR)}\Big/\sum\frac{1}{\mathrm{Var}(\ln RR)}$$

and for the variance

$$\mathrm{Var}(\ln RR)=\frac{1}{\sum\frac{1}{\mathrm{Var}(\ln RR)}}.$$

The overall value for the ln RR in all of the studies combined was obtained using the same method that was used to pool results from the prospective studies, using the overall values for the case-control and prospective studies.

Can Fybogel sachets (Ispaghula husk) be taken indefinitely?

I know of no documented or anecdotal evidence of long term ill effects from taking ispaghula over many years. The only theoretical problem is of reduced calcium absorption which might lead to an increased risk of osteoporosis. Faecal calcium excretion is increased by any form of extra fibre; a short term study showed such an increase during the ingestion of ispaghula and of bran but the changes did not reach statistical significance.[1] It is unlikely that this would be an adverse effect of any practical importance.—JOHN R BENNETT, consultant physician, Kingston upon Hull.

1 Smith RG, Rowe MJ, Smith AN, *et al*. A study of bulking agents in elderly patients. *Age and Ageing* 1980;9:267-71.

Can non-steroidal anti-inflammatory drugs cause tinnitus?

Tinnitus has been reported as a side effect of treatment with most, if not all, non-steroidal anti-inflammatory drugs. Most of the reports have been on clinical trials rather than as well documented case reports. The Committee On Safety Of Medicines has had a few reports with most non-steroidal anti-inflammatory drugs. The incidence appears to be low, and there is no good evidence that one non-steroidal anti-inflammatory drug is more likely to have this effect than another. In some cases tinnitus has been accompanied by sensorineural deafness which is usually reversible though one case of irreversible deafness has been reported with piroxicam.[1] I was unable to find any studies of the mechanism of this effect, but aspirin produces dose related cochlear toxicity characterised by depolarisation of the cochlear apparatus with reduced hearing over the whole frequency range.[2]—LINDA BEELEY, consultant clinical pharmacologist, Birmingham.

1 Varnick DM, Kelly JH. Sudden hearing loss associated with piroxicam. *Am J Otol* 1986;7:97-8.
2 Dukes MNG, ed. *Meyler's side effects of drugs*. 10th ed. Amsterdam-New York-Oxford: Elsevier, 1984:143.

Correction

Severe hypermagnesaemia due to magnesium sulphate enemas in patients with hepatic coma

We regret that an error occurred in this paper by Dr P O Collinson and Dr A K Burroughs (18 October, p 1013). In figure 2 it is stated that calcium is represented by blocked circles and magnesium by blocked squares. It should have said that calcium is represented by blocked squares and magnesium by blocked circles.

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Guest Editorial — William J. Blot [1,2] and Joseph F. Fraumeni, Jr. [1]

Passive Smoking and Lung Cancer [3]

Passive smoking, the inhalation of smoke from tobacco products used by others, was first associated with human cancer in 1981 when two publications reported higher rates of lung cancer among nonsmoking women married to smokers (*1*, *2*). The findings were greeted with some skepticism, in part because of questions raised about the methods used, but mostly because it was thought unlikely that nonsmokers would receive sufficient smoke exposure to more than double their risk of lung cancer as these reports suggested. Considerable evidence has accumulated in the interim, so that a review of the topic now seems timely to summarize where we stand and to help identify new avenues of research on passive smoking and cancer. This review is restricted to lung cancer, since information to assess the potential effect of passive smoking on other cancers is still inadequate. We first comment on the individual epidemiologic studies evaluating passive smoking, then combine data to provide a summary estimate of the RR of lung cancer among nonsmoking women married to smokers. Difficulties in exposure assessment are examined, then taken into account in our assessment of the passive smoking-lung cancer relation.

INITIAL STUDIES

The reports of Hirayama from Japan (*1*) and Trichopolous et al. from Greece (*2*) showing increases in lung cancer risk among nonsmoking women married to smokers were derived from two different types of epidemiologic investigation. The study in Japan used the cohort approach, in which death rates for various diseases were determined among 265,000 persons comprising 95% of the population aged 40–59 in 29 health center districts. For each of these individuals a 1-page questionnaire had been completed in 1965, indicating whether the individual was a cigarette smoker and how many cigarettes per day he or she smoked. For the period 1965–81, 200 lung cancer deaths were recorded among nonsmoking married women, with death rates increasing in proportion to the amount of cigarettes smoked by their husbands in 1965 (*3*, *4*). Table 1 describes the trend, indicating a 90% excess in lung cancer among nonsmoking females whose husbands smoked 20 or more cigarettes per day. No increase in mortality from other cancers, except for nasal and brain tumors, was detected in this group. Among nonmalignant diseases, the excess in death rates for emphysema-chronic bronchitis reached 60% among women married to heavy smokers, with a similar but less steep trend for ischemic heart disease. For no major disease, however, was the association with passive smoking as marked as for lung cancer.

The study in Greece was a hospital-based case-control investigation of lung cancer (*2*, *5*, *6*). Cases were women with lung cancers other than adenocarcinoma admitted to one of the three largest hospitals treating respiratory cancer in Athens, while controls were selected from a single Athens orthopedic hospital. Interviews with the subjects revealed 77 cases and 225 controls who had not smoked cigarettes. Among these nonsmoking women, RRs of lung cancer were higher for those married to smokers than for those married to nonsmokers, long-term ex-smokers, or never married women and tended to increase according to amount smoked by the husband (table 2).

Some criticism of the reports quickly surfaced (*7–10*). Neither study evaluated exposure to environmental tobacco smoke outside the home. A potential statistical error was noted in the Hirayama report, although its impact was negligible (*7–9*). The Hirayama article provided only meager details of the methods used in the conduct and analysis, so some questions were raised about the cohort and its follow-up. Subsequent reports by Hirayama (*3*, *4*, *11*) still omit detailed discussion of study design, but several aspects of the investigation weigh against the possibility that inherent biases account for the elevated risk observed with passive smoking. These include the prospective nature of the study, with information on smoking obtained prior to the follow-up for cancer deaths; the dose-response relation evident via internal comparisons, with death rates for segments of the cohort (nonsmoking women married to light, moderate, or heavy smokers) progressively higher than rates in another segment of the same cohort (nonsmoking women married to nonsmokers); and the completeness of ascertainment of mortality available through the Japanese national system of mortality registration, so that

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ABBREVIATIONS USED: CI = confidence interval; RR = relative risk.

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[3] Received March 28, 1986.

Editor's note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes, cure, or prevention of cancer.

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TABLE 1.—*Ratios of lung cancer mortality, 1966–81, among nonsmoking Japanese females according to the smoking habits of their husbands*[a]

Husband's smoking status	No. of lung cancer deaths	Mortality ratios	90% CI
Nonsmoker	37	1.0	—
Ex-smoker	17	1.4	0.9–2.2
1–14 cigarettes/day	58	1.4	1.0–2.0
15–19 cigarettes/day	24	1.5	1.0–2.4
≥20 cigarettes/day	64	1.9	1.3–2.7

[a] Data from (*3*).

virtually all deaths could be identified among the various subgroups of the cohort. Determination of cause of death was not described in the Hirayama publications, and it is suspected that the lung cancers reported for many of the women may have been diagnosed solely on clinical or radiologic evidence. There is no reason to suspect, however, that diagnostic differentials exist according to the smoking status of the husband. Histologic confirmation was also not obtained on all patients in the Greek study, and the cases and controls were derived from different hospitals (although both groups were similar on demographic and socioeconomic grounds). Despite their limitations, the studies of Hirayama and Trichopoulos et al. yielded remarkably consistent results and served to stimulate additional research to evaluate environmental tobacco smoke as a risk factor for cancer.

RECENT EPIDEMIOLOGIC INVESTIGATIONS

Since 1981 several studies in the United States (table 3) and abroad (table 4) have assessed lung cancer risk among persons exposed to environmental tobacco smoke. Few were designed specifically to evaluate passive smoking and thus typically obtained only limited exposure information. In combination, however, they provide some clarification of the patterns of risk among passive smokers.

American Cancer Society Study

The first report subsequent to the Japanese and Greek investigations was based on existing data from the American Cancer Society's cohort mortality study. Garfinkel (*12*) identified 176,000 married women throughout the United States who indicated in a questionnaire administered in 1959 that they had never smoked cigarettes regularly and for whom information on their husband's smoking habits was available. A total of 153 lung cancer deaths were recorded during 1960–72 among this group. Small elevations in lung cancer mortality were found among women married to light (RR = 1.3) or heavy (RR = 1.1) smokers compared to women married to nonsmokers. These findings were largely interpreted as refuting the earlier studies, particularly since the author concluded that "nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer." However, the RR estimates were above 1.0 and the 95% confidence limits associated with husband's smoking were large enough (0.9–1.9 for light smokers; 0.8–1.6 for heavy smokers) to accommodate a small to moderate effect of passive smoking.

TABLE 2.—*RRs of lung cancer other than adenocarcinoma among nonsmoking Greek women according to the smoking habits of their husbands*[a]

Husband's smoking status	Cases	Controls	RR	95% CI
Nonsmoker	24	109	1.0	—
Ex-smoker	15	35	1.9	0.9–4.1
1–20 cigarettes/day	24	56	1.9	1.0–3.7
≥21 cigarettes/day	14	25	2.5	0.9–7.0

[a] Data from (*5, 6*).

Other Studies in the United States

Six case-control studies that estimated lung cancer risks for passive smoking among nonsmokers have recently been completed in different areas of the United States. Most had relatively small numbers of cases, since the great majority of lung cancers in this country occur among smokers. They also tended to focus on women, as there were even fewer nonsmoking men with lung cancer available for investigation.

In a hospital-based investigation into the elevated lung cancer mortality rates among Louisiana's southern parishes (*13*), only 10 male lung cancer patients (of a total of over 1,000) and 25 ever-married female cases (of 302) had never smoked cigarettes. After 4 cases were excluded because of inadequate information on spouse's smoking habits, a twofold increased risk of lung cancer was found for both male and female nonsmokers whose spouses smoked compared to those whose spouses did not smoke. The excess was threefold for those whose spouses smoked more than 2 packs per day. Some increase in risk was also noted among male smokers whose mothers had smoked, but no association was found for paternal smoking.

TABLE 3.—*RRs of lung cancer among nonsmoking women married to smokers reported from epidemiologic studies in the United States*

Study,[a] author (reference)	Spouse smoked	Cases	Controls	RR	95% CI
Garfinkel (*12*)	No	65	—[a]	1.2	0.8–1.6
	Yes	88			
Correa et al. (*13*)	No	8	72	2.1	0.8–5.5
	Yes	14	61		
Kabat and Wynder (*15*)	No	11	10	0.8	0.3–2.5
	Yes	13	15		
Wu et al. (*16*)	No	9	19	1.2	0.6–2.5
	Yes	19	33		
Garfinkel et al. (*18*)	No	43	148	1.2	0.9–1.6
	Yes	91	254		

[a] All investigations were case-control studies, except the first, which was a cohort study ascertaining lung cancer deaths over a 6-yr period among 176,000 women.

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TABLE 4.—*RRs of lung cancer among nonsmoking women married to smokers reported from case-control studies in other countries*

Study, author (reference)	Country	Spouse smoked	Cases	Controls	RR	95% CI
Akiba et al. (*20*)	Japan	No	21	82	1.5	0.9-2.6
		Yes	73	188		
Chan et al. (*21*)	Hong Kong	No	50	73	0.8	0.4-1.3
		Yes	34	66		
Koo et al. (*23*)	Hong Kong	No	35	70	1.5	0.9-2.7
		Yes	51	66		
Lee et al. (*25*)	Great Britain	No	5	16	1.6	0.5-5.0
		Yes	19	38		
Pershagen et al. (*26*)	Sweden	—[a]	67	134	1.2	0.6-2.1

[a] Data in (*26*) not presented separately by smoking status of spouse.

Dalager et al. (*14*) subsequently added data on 14 male cases from a case-control study in New Jersey to the Louisiana data and noted that the trend toward increasing risk associated with number of cigarettes smoked per day by the spouse was stronger for squamous cell carcinoma than for adenocarcinoma of the lung. When information from a case-control study of lung cancer in Texas was included, the total number of cases who had never used tobacco products was raised to 99. The only exposure variable available for all these subjects was duration of living with a household member (parent, spouse, or other individual) who smoked. There was no increase in risk (RR=0.8; 95% CI=0.5-1.3) associated with ever living with a smoker, but a slight increase (RR=1.2; 95% CI=0.6-2.5) was found when the duration of exposure exceeded 40 years.

In a multicenter case-control study, Kabat and Wynder (*15*) reported that among 36 nonsmoking male and female lung cancer patients, the proportion of smoking spouses was not higher than expected (RR=0.9; 95% CI=0.3-2.1). The authors did not present risk estimates according to the number of cigarettes smoked by the spouse. Among nonsmoking males, an increased risk of lung cancer (RR=3.3; 95% CI=1.0-10.5) was reported for those exposed to tobacco smoke at work.

Wu et al. (*16*) noted 20 and 30% increases in the risk of adenocarcinoma of the lung among nonsmoking women in Los Angeles who were exposed to passive smoking from spouses or at work, respectively. Interviewed were 29 nonsmoking patients and 62 nonsmoking controls. Only 2 nonsmoking patients had squamous cell cancers, precluding evaluation of risks for this type of lung cancer. Combining years exposed at home or at work, the increase in risk of lung adenocarcinoma rose to twofold for those in the highest duration of exposure category, although the trend was not statistically significant. No increase in adenocarcinoma among nonsmokers was associated with exposure to parental tobacco smoking during childhood, but having a mother or father who smoked yielded RR estimates of 1.7 and 1.5, respectively, among the total group, most of whom were smokers.

In a hospital-based case-control investigation in North Carolina (*17*) designed to explore the effect of passive smoking on many cancers, 22 patients had lung cancer. There was a 50% increase in risk (95% CI=0.6-4.3) of this tumor among persons married to smokers. All but 2 of the lung cancer patients were smokers themselves, however, limiting the study's ability to assess an association with passive smoking.

Garfinkel et al. (*18*) carried out the largest case-control study assessing passive smoking to date. In a hospital-based investigation in New Jersey and Ohio, nonsmoking women with lung cancer (134 cases) were matched to nonsmoking women with colorectal cancer (402 controls). Information was sought from the subjects, or more often their next of kin, not only on spouse's smoking habits, but also on exposures to passive smoking outside the home. There was no evidence of a trend of increasing risk of lung cancer with increasing hours per day of exposure to passive smoking. More cases than controls, however, were found to have husbands who had smoked. The overall excess was 20% (RR=1.2; 95% CI=1.0-1.7) and increased to 100% (RR=2.0; 95% CI=1.1-3.5) among those whose husbands smoked 2 or more packs of cigarettes per day. The RR estimates tended to be slightly higher when husband's smoking was categorized according to cigarettes smoked at home. This study is unusual in that the hospital control group consisted of admissions for a single disease entity rather than a variety of conditions. Hence case-control differences might reflect unusual characteristics of colorectal cancer as opposed to lung cancer. Colorectal cancer is unrelated to smoking habits (*19*) and presumably to passive smoking, so the controls used should be appropriate.

Studies in Other Countries

Several recent publications have evaluated the relation of passive smoking to lung cancer in other countries, mainly through case-control studies (table 4). Utilizing data from a case-control study of lung cancer among a cohort of atomic bomb survivors in Hiroshima and Nagasaki, Akiba et al. (*20*) found a 50% increase in the risk of lung cancer among nonsmoking women whose husbands smoked. There was a progressive increase in risk with amount smoked by the husband, the excess reaching twofold for women married to men who smoked 30 or more cigarettes per day. A reduction in lung cancer risk was also reported following cessation of exposure to husband's smoking. The findings, based on 94 nonsmoking cases and 270 nonsmoking controls, are

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quantitatively very similar to those reported in the Hirayama cohort study (*3, 4*), despite different populations covered and different methods employed. Most of the interviews were with the next of kin of deceased cases and controls, but the information on smoking habits closely resembled that obtained from the women themselves during routine surveys of atomic bomb survivors in the 1960's. This comparison provided independent confirmation by the relative of the nonsmoking status of most of the women, both cases and controls, arguing against the possibility that Japanese women tend to report themselves as nonsmokers when they actually smoke.

In Hong Kong, where the rates of lung cancer among females are high by world standards, two investigations provided mixed results. Chan et al. (*21, 22*) reported that 41% of nonsmoking female cases versus 48% of orthopedic controls were passive smokers, although the criteria used to define exposure are not clear. Seeking information on lifetime exposure to environmental tobacco smoke in the home and workplace, Koo et al. (*23*) interviewed 88 nonsmoking women with lung cancer and 137 nonsmoking neighborhood-matched controls. The RR of lung cancer among women married to husbands who smoked in their presence was 1.5 (95% CI=0.9-2.7), rising slightly among those who were exposed to environmental tobacco smoke either at home or at work compared to those not exposed at either setting (Koo LC: Personal communication). There was no increasing trend with amount smoked, however, and the total number of hours of exposure per year from all sources of passive smoking was somewhat less for the cases than controls. When risk estimates were calculated according to cell type, an increase in risk associated with passive smoking was more apparent for squamous cell cancer than adenocarcinoma of the lung.

Limited information on this issue is available from western Europe. A case series of 39 female nonsmoking lung cancer patients in the Federal Republic of Germany was described by Knoth et al. (*24*). About 60% were reported to live with smokers. No control group was used, but the authors referred to census statistics indicating that only 22% of males aged 50-69 were smokers. The appropriateness of this comparison is doubtful, because of likely differences in the definition of smoking status (e.g., the census ascertained current smoking prevalence at a fixed point in time, whereas apparently no such time restriction was placed on the cases) and because some of the patients may have lived with more than a single individual.

As part of a hospital-based case-control study in Great Britain, Lee et al. (*25*) interviewed 47 married lung cancer patients and 96 controls admitted for conditions unrelated to smoking, who had never smoked. Information on spouse's smoking habits was sought from the study subjects and the spouses themselves. The RR of lung cancer among nonsmoking women married to smokers was 1.6 (95% CI=0.4-5.6) when smoking habits during marriage were reported by the husbands and 1.0 (95% CI=0.2-4.4) among nonsmoking men whose wives reported themselves as smokers. The RRs were lower for women and higher for men when data from the subjects but not the spouses were used.

Among 2 cohorts of nonsmoking Swedish women, incident cases of lung cancer plus controls were identified during 1963-80 (*26*). Questionnaires completed in 1984 on 67 patients or their next of kin and about four times as many age-matched controls provided information on the spouse's smoking habits. There was little overall increased risk of lung cancer among women married to smokers, but a 2.5-fold excess (95% CI= 1.0-6.7) was found for Kreyberg I lung cancer, predominantly squamous and oat cell carcinomas. For both Kreyberg type I and II lung cancers, risks were most elevated for the heavy-exposure group, namely, those married to men who smoked more than 15 cigarettes per day during 30 or more years of marriage.

Only limited information is available from cohort studies conducted since the observations of Hirayama (*1*) and Garfinkel (*12*). In a follow-up survey in Scotland, Gillis et al. (*27*) noted excess lung cancer mortality among nonsmoking males but not females exposed to passive smoking, but the numbers involved were quite small (6 male and 8 female lung cancer deaths).

SUMMARY RR ESTIMATES

We combined results from the epidemiologic studies listed in tables 3 and 4 with those of Hirayama (*3*) and Trichopoulos et al. (*5, 6*), weighting the RRs from each study according to the Mantel-Haenszel procedure (*28*). **Based on the overall data, the summary RR estimate of lung cancer among nonsmoking women whose husbands smoked was 1.3 (95% CI=1.1-1.5).**

As reported in several investigations evaluating dose-response trends, the RR estimates tend to be higher for women married to heavy smokers (table 5). Although the definition of a heavy smoker varied across the studies, if results for the high exposure categories are combined, the summary RR estimate of lung cancer associated with heavy passive smoking is 1.7 (95% CI=1.4-2.1).

TABLE 5.—*RRs of lung cancer among nonsmoking women, according to number of cigarettes smoked per day by their husbands, reported from epidemiologic studies in the United States and other countries*

Study, author (reference)	Husband's smoking status		
	Nonsmoker	Light	Heavy*
Garfinkel (*12*)	1.0	1.3	1.1
Correa et al. (*13*)	1.0	1.2	3.5
Wu et al. (*16*)	1.0	1.2	2.0
Garfinkel et al. (*18*)	1.0	1.1	2.0
Akiba et al. (*20*)	1.0	1.4	2.1
Koo et al. (*23*)	1.0	1.9	1.2
Pershagen et al. (*26*)	1.0	1.0	3.2

* Heavy smokers are defined as those who smoked ≥20 cigarettes per day in (*12*) and (*25*); ≥30 cigarettes per day in (*20*); ≥40 cigarettes per day in (*13*) and (*18*); ≥15 cigarettes per day among those married at least 30 yr in (*26*); and as those with ≥30 yr of passive smoking exposure in (*16*).

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The cumulative epidemiologic evidence to date thus suggests that nonsmokers married to smokers experience a small to moderate increased risk of lung cancer. There is uncertainty, however, about the causal nature of the association, especially in view of limitations in assessing exposure to environmental tobacco smoke.

EXPOSURE ASSESSMENT

While women married to smokers tend to receive greater exposure to ambient smoke than women married to nonsmokers, it is apparent that husband's smoking status is an imperfect correlate of total exposure to environmental tobacco smoke. Such was suggested by a survey of 35,000 nonsmoking male and female participants of a health maintenance organization in San Francisco and Oakland who answered questions regarding their hours of exposure to environmental tobacco smoke at home, in office rooms and other confined spaces, or in larger areas outside the home (*29*). It was found that nearly one-half of the female nonsmokers married to smokers reported no exposure to passive smoking in the home, while about one-third of the women married to nonsmokers reported some passive smoking outside the home. Although the survey focused on current exposures and included many young adults, whose practices are not necessarily those of women in the 55–70 age range where lung cancer usually arises, it appears that information on husband's smoking habits yields only an approximate measure of environmental tobacco smoke within the home and a crude indication of total exposure. **The survey did reveal, however, that even today the spouse is the dominant source of passive smoking exposure among nonsmokers who are married to smokers.**

Although interviews have been the method of ascertaining exposure to ambient tobacco smoke, there is mounting interest in supplementing self-reported information with more objective measures based on laboratory assessment of tobacco smoke aerosols and biological specimens obtained from nonsmokers. Biochemical assessment of passive smoking is complicated by the presence of over 3,000 substances that have been detected in tobacco and its combustion products, including a great number and variety of carcinogens, cocarcinogens, promoting agents, and mutagens (*19, 30*), many of which tend to vary in concentration between mainstream and sidestream smoke. Mainstream smoke arises during puffs and passes through the butt end of the cigarette, whereas sidestream smoke is generated by the passive burning of the cigarette and is emitted directly into the air. Since about 80% of the tobacco is usually burned between puffs, indoor pollution from environmental tobacco smoke comes mainly from sidestream smoke, with exhaled mainstream smoke making the smaller contribution (*31*). Table 6 lists some of the constituents that have been found in the air of smoke-filled rooms in homes, offices, restaurants, and bars and provides ratios of the levels of the substances in sidestream versus mainstream cigarette smoke determined under experimental conditions. As indicated in the table, some components such as the nitrosamines and various particulates occur in much greater concentrations in sidestream smoke. In addition, sidestream smoke may increase exposure to other respiratory carcinogens, including radon and its daughter products (*32*). In Sweden radon levels in the households of smokers were more than double those of nonsmokers, possibly because ambient tobacco smoke increases the number of particulates to which radon products can cling.

TABLE 6.—*Selected constituents of tobacco smoke and their approximate ratio in sidestream to mainstream smoke*[a]

Constituent	Ratio in sidestream to mainstream smoke
Nitrosamines	5–437
Ammonia	73–150
Formaldehyde	50
2-Naphthylamine	39
Aniline	30
Nickel	0.2–31
Acrolein	12
Carbon dioxide	8
Cadmium	4–7
Carbon monoxide	2–5
Methane	3
Nicotine	2–3
Benzo[α]pyrene	2–3
Phenol	3
Tar	1–2
Acetylene	0.8
Hydrogen cyanide	0.05–0.4

[a] Adapted from (*19, 30, 31, 53*).

Although cigarette smokers obviously inhale considerably greater amounts of tobacco smoke than can be achieved by involuntary inhalation of smoke, the exposures to particular agents from passive versus active smoking have not been fully characterized (*33*). Some comparative estimates have been made, however. One, based on experimentally determined air measurements, estimated that airborne levels of aldehyde, total particulate matter, and nicotine inhaled by passive smoking in 1 hour would be, respectively, about 1/4, 1/11, and 1/50 the levels inhaled by smoking 1 cigarette (*34*). On the other hand, the amount of volatile nitrosamines inhaled by a passive smoker in 1 hour in a closed environment, such as a commuter train bar, was reported as equivalent to that received by smoking over one-half pack of filter cigarettes (*35*). Repace and Lowrey (*36*) estimated a range of 0–14 mg tar/day (average, 1.4 mg) received by nonsmokers, corresponding to the tar obtained from smoking about 0.1–1 cigarette. Contributing to the difficulty of assessing exposure to lung tissue are different routes of exposure, with passive smokers generally inhaling through nasal passages, as opposed to the mouth and throat among direct smokers. Little is known about the deposition of tobacco smoke aerosols within the bronchus and lung, although deposition fractions have been reported to be less for sidestream than mainstream smoke (*37*). Somewhat smaller particle sizes have been measured for sidestream smoke (*31*), suggest-

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ing that a greater proportion of the exposure from passive smoking reaches the more distal portions of the lungs.

The biochemical assessments perhaps most relevant to environmental tobacco smoke exposure have involved assays of smoke constituents or their metabolites in body fluids. Saliva, blood, and urine specimens have been collected from passive smokers for determinations of several substances, including nicotine and cotinine, the major metabolite of nicotine. Hoffmann et al. (*38*) exposed 10 nonsmoking volunteers for 80 minutes in an experimentally controlled room to steady-state pollution from 4 standard cigarettes and almost immediately observed sharp rises in salivary nicotine, with subsequent tripling of salivary, plasma, and urinary cotinine levels, but little change in thiocyanate or carboxyhemoglobin. Elevated cotinine levels among passive smokers have been a consistent finding in other experimental studies, as well as in naturally occurring settings (*39*). Wald et al. (*40*) noted a tenfold gradient in urinary cotinine among 199 nonsmokers, with levels rising in proportion to duration of exposure to environmental tobacco smoke in the week prior to urine collection. Similar trends have been observed in other surveys of nonsmoking adults in Great Britain and Japan (*41, 42*) and in a population-based sampling of 569 British school children (*43*). Mean urinary cotinine concentrations among North Carolina infants living with smokers were over 20 times higher than the corresponding levels among infants whose parents did not smoke (*44*). The levels also tended to increase with the number of cigarettes the mother smoked in the preceding 24 hours.

These studies leave little doubt that nonsmokers actually inhale and metabolize sidestream smoke constituents. The levels of most substances, such as cotinine, in passive smokers appear to be much less than in smokers themselves. The cotinine concentrations among passive smokers are generally about 1/100 or less those of direct smokers, although the fraction is much higher in Japan (*42*). In the two surveys of adults comparing "heavy" passive to active smoking, the fractions were 1/50 in Great Britain (*40*) and 1/7 in Japan (*42*). Translating these figures into cigarette equivalents suggests that nonsmokers heavily exposed to environmental tobacco smoke receive nicotine in amounts similar to those obtained by smoking between 1/2 and 3 cigarettes per day. The lower level probably reflects the situation in the United States, while the higher fraction in Japan may be influenced by greater degrees of crowding and smaller average room sizes. Hence, if involuntary smoking exposures to nicotine approximate those to the carcinogens in tobacco smoke, then the risks of lung cancer associated with passive smoking might be estimated by assuming that heavy passive smoking is equivalent to smoking about 1 cigarette every other day. This may be an underestimate, however, since ingredients in tobacco smoke other than nicotine appear responsible for smoking-induced lung cancer, and passive smokers inhale comparatively less nicotine than several other substances, including nitrosamines. Thus passive smoking might result in exposures to specific carcinogens in ambient tobacco smoke equivalent to smoking up to a few cigarettes per day.

Precise estimates of the risk of lung cancer associated with smoking 1 or 2 cigarettes per day are not available, since not many smoke so few cigarettes daily. However, three major prospective cohort studies of mortality among smokers [the American Cancer Society's investigation of nearly 500,000 men (*45*); the 16-yr follow-up of 250,000 U.S. veterans (*46*); and the 20-yr follow-up of 34,000 British doctors (*47*)] revealed RRs of lung cancer of 4.6, 4.8, and 7.8 among smokers of 1–9, 1–9, and 1–14 cigarettes per day, respectively. Linear interpolation between these values and the base-line level of 1.0 for nonsmokers would yield estimated RRs for smokers of a few cigarettes per day of 1.5-fold to twofold, the same order of increase associated with high levels of passive smoking.

EVALUATING CAUSAL SIGNIFICANCE

The evidence from epidemiologic investigations suggests that nonsmoking women married to smokers have experienced an increase in lung cancer risk. Our calculations summarizing the available data place the excess at about 30%. Since environmental tobacco smoke contains many agents that may contribute to pulmonary carcinogenesis and since constituents of tobacco smoke have been detected in body fluids of passive smokers, it is biologically plausible that a causal relation exists between passive smoking and lung cancer. This interpretation is enhanced by the replication of findings in different populations around the world, by a dose-response effect with excess risks of about 70% among nonsmokers heavily exposed to ambient tobacco smoke, by cell type predilections resembling those associated with direct smoking, and by the similarity in risk estimates between heavy passive smokers and exceptionally light active smokers.

The current evidence, however, must still be interpreted with caution. It has been difficult to quantify actual exposure to environmental tobacco smoke, and estimates based on smoking habits of spouses are relatively crude approximations. There is also concern that women married to smokers differ from women married to nonsmokers in ways that influence lung cancer risk. In the passive smoking survey of San Francisco and Oakland (*29*), the reported passive smoking exposures from all sources were higher for whites, the young, those without a college education, heavy drinkers of alcoholic beverages, and workers exposed to hazardous substances. Race, age, and education were usually controlled for in the design or analysis of the studies reviewed, however, and alcohol is not generally recognized as an independent risk factor for lung cancer (*48*). Occupational exposure to respiratory carcinogens (*49*) may occur among women married to smokers, but the numbers would be very small and not likely to confound the relationships observed. There is evidence that intake of foods high in beta-carotene and other nutrients may lower the risk of lung cancer (*50*). It is not known

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whether women married to smokers consume less of these foods, but adjustment for intake of green vegetables and other vitamin A-containing foods in two studies of passive smoking (*3*, *14*) had little effect on the estimates of lung cancer risk.

More extensive and innovative studies are needed to evaluate and clarify the causal nature of the relation between lung cancer and passive smoking. Although attention will probably continue to center on nonsmoking women married to smokers, the group most likely to provide the largest amount of relevant data, special efforts should be made to quantify more precisely the exposure levels to ambient tobacco smoke both within and outside the home. Larger studies will be required to assess fully the small increases in RR expected from passive smoking, confirm trends of greater risk with higher levels of exposure, adequately adjust for confounding factors, and search for interactions with host susceptibility (e.g., genetic or nutritional measures). The impact of transplacental and early life exposures to parental smoking should also be investigated as a risk factor that might, as suggested by animal models, potentiate the effects of later exposure to tobacco smoke or other carcinogenic hazards (*13*). The tendency for lung cancer to aggregate in families (*51*) should be investigated to identify the possible role of passive smoking as well as genetic susceptibility. In addition, there is potential for other long-term consequences such as coronary artery disease (*52*), indicating the importance of further research to clarify the role of passive smoking on the risk of various chronic diseases. Whenever possible, epidemiologic evaluation of passive smoking should incorporate laboratory measures of tobacco smoke components and their by-products, plus indicators of biologic response and interactions.

CONCLUSION

Further research is needed to evaluate the etiologic role of passive smoking; however, **it would seem prudent to regard the existing evidence as highly suggestive that long-term exposure to environmental tobacco smoke increases the risk of lung cancer.**

REFERENCES

(*1*) HIRAYAMA T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. Br Med J 1981; 282:183–185.

(*2*) TRICHOPOULOS D, KALANDIDI A, SPARROS L, et al. Lung cancer and passive smoking. Int J Cancer 1981; 27:1–4.

(*3*) HIRAYAMA T. Lung cancer in Japan: Effects of nutrition and passive smoking. In: Mizell M, Correa P, eds. Lung cancer: Causes and prevention. Deerfield Beach, FL: Verlag Chemie, 1984: 175–195.

(*4*) ———. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 1984; 13:680–690.

(*5*) TRICHOPOULOS D, KALANDIDI A, SPARROS L. Lung cancer and passive smoking: Conclusion of Greek study. Lancet 1983; 2:677–678.

(*6*) TRICHOPOULOS D. Passive smoking and lung cancer. Lancet 1984; 1:684.

(*7*) KORNEGAY HR, KASTENBAUM MA. Non-smoking wives of heavy smokers have a higher risk of lung cancer. Br Med J 1981; 283:914.

(*8*) MANTEL N. Nonsmoking wives of heavy smokers have a higher risk of lung cancer. Br Med J 1981; 283:914–915.

(*9*) HARRIS JE, DUMOUCHEL WH. Nonsmoking wives of heavy smokers have a higher risk of lung cancer. Br Med J 1981; 283:915.

(*10*) MACDONALD EJ. Nonsmoking wives of heavy smokers have a higher risk of lung cancer. Br Med J 1981; 283:915–916.

(*11*) HIRAYAMA T. Nonsmoking wives of heavy smokers have a higher risk of lung cancer. Br Med J 1981; 283:916–917.

(*12*) GARFINKEL L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. JNCI 1981; 66: 1061–1066.

(*13*) CORREA P, PICKLE LW, FONTHAM E, et al. Passive smoking and lung cancer. Lancet 1983; 2:595–597.

(*14*) DALAGER NA, PICKLE LW, MASON TJ, et al. The relation of passive smoking and lung cancer among non-tobacco users. Cancer Res 1986; 46:4808–4811.

(*15*) KABAT GC, WYNDER EL. Lung cancer in nonsmokers. Cancer 1984; 53:1214–1221.

(*16*) WU AH, HENDERSON BE, PIKE MC, et al. Smoking and other risk factors for lung cancer in women. JNCI 1985; 74:747–751.

(*17*) SANDLER DP, EVERSON RB, WILCOX AJ. Passive smoking in adulthood and cancer risk. Am J Epidemiol 1985; 121:37–48.

(*18*) GARFINKEL L, AUERBACH O, JOUBERT L. Involuntary smoking and lung cancer: A case-control study. JNCI 1985; 75:463–469.

(*19*) U.S. Department of Health and Human Services. The health consequences of smoking: Cancer. A report of the Surgeon General. Washington, DC: U.S. Govt Print Off, 1982 [DHHS publication No. (PHS)82-50179].

(*20*) AKIBA S, KATO H, BLOT WJ. Passive smoking and lung cancer among Japanese women. Cancer Res 1986; 46:4804–4807.

(*21*) CHAN WC, COLBOURNE MJ, FUNG SC, et al. Bronchial cancer in Hong Kong 1976–1977. Br J Cancer 1979; 39:182–192.

(*22*) CHAN WC, FUNG SC. Lung cancer in non-smokers in Hong Kong. In: Grundmann E, ed. Cancer epidemiology. New York: Gustav Fisher Verlag, 1982:199–202.

(*23*) KOO LC, HO JH, SAW D. Is passive smoking an added risk factor for lung cancer in Chinese women? J Exp Clin Cancer Res 1984; 3:277–283.

(*24*) KNOTH A, BOHN H, SCHMIDT F. Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen. Med Klin 1983; 78:66–69.

(*25*) LEE PN, CHAMBERLAIN J, ALDERSON MR. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 1986; 54:97–105.

(*26*) PERSHAGEN G, HRUBEC Z, SVENSSON C. Passive smoking and lung cancer in Swedish women. Am J Epidemiol. In press.

(*27*) GILLIS C, HOLE D, HAWTHORNE V, et al. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Respir Dis 1984; 65 (suppl 133):121–126.

(*28*) ROTHMAN KJ, BOICE JD, JR. Epidemiologic analysis with a programmable calculator. Washington, DC: U.S. Govt Print Off, 1979 [DHEW publication No. (NIH)79-1649].

(*29*) FRIEDMAN GD, PETITTI DB, BAWOL RD. Prevalence and correlates of passive smoking. Am J Public Health 1983; 73:401–405.

(*30*) TRIEBIG G, ZOBER MA. Indoor air pollution by smoke constituents—a survey. Prev Med 1984; 13:570–581.

(*31*) STOBER W. Lung dynamics and uptake of smoke constituents by nonsmokers. Prev Med 1984; 13:589–601.

(*32*) BERGMAN H, AXELSON O. Passive smoking and indoor radon daughter concentrations. Lancet 1983; 2:1308–1309.

(*33*) FIRST MW. Constituents of sidestream and mainstream tobacco smoke and markers to quantify exposure to them. In: Gammage R, Kaye S, eds. Indoor air and human health. Chelsea, MI: Lewis Publ, 1985:195–204.

(*34*) HUGOD C. Indoor air pollution with smoke constituents: An experimental investigation. Prev Med 1984; 13:582–588.

(*35*) BRUNNEMANN KD, ADAMS JD, HO DP, et al. The influence of tobacco smoke on indoor atmospheres. II. Volatile and tobacco-specific nitrosamines in main and sidestream smoke and their

2023381864

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contribution to indoor pollution. In: Proceedings of the fourth joint conference on sensing of environmental pollutants. Washington, DC: American Chemical Society, 1978:876–880.
(36) REPACE JL, LOWREY AH. A quantitative estimate of nonsmokers' lung cancer risk from passive smoking. Environ Int 1985; 11:3–22.
(37) HILLER FC. Deposition of sidestream cigarette smoke in the human respiratory tract. Prev Med 1984; 13:602–607.
(38) HOFFMANN D, HALEY N, ADAMS JD, et al. Tobacco sidestream smoke: Uptake by nonsmokers. Prev Med 1984; 13:608–617.
(39) SCHIEVELBEIN H, RICHTER F. The influence of passive smoking on the cardiovascular system. Prev Med 1984; 13:626–644.
(40) WALD NJ, BOREHAM J, BAILEY A, et al. Urinary cotinine as marker of breathing other people's tobacco smoke. Lancet 1984; 1:230–231.
(41) JARVIS MJ, TUNSTALL-PEDOE H, FEYERBAND C, et al. Biochemical markers of smoke absorption and self reported exposure to passive smoking. J Epidemiol Community Health 1984; 38: 335–339.
(42) MATSUKURA S, TAMINATO T, KITANO N, et al. Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers. N Engl J Med 1984; 311:828–832.
(43) JARVIS MJ, RUSSELL MA, FEYERBAND C, et al. Passive exposure to tobacco smoke: Saliva cotinine concentrations in a representative population sample of non-smoking school children. Br Med J 1985; 291:927–929.
(44) GREENBERG RA, HALEY NJ, ETZEL RA, et al. Measuring the exposure of infants to tobacco smoke. N Engl J Med 1984; 310:1075–1078.
(45) HAMMOND EC. Smoking in relation to the death rates of one million men and women. Natl Cancer Inst Monogr 1966; 19: 127–204.
(46) ROGOT E, MURRAY JL. Smoking and causes of death among US veterans: 16 years of observation. Public Health Rep 1980; 95:213–222.
(47) DOLL R, PETO R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 1976; 2: 1525–1536.
(48) FRAUMENI JF JR, BLOT WJ. Lung and pleura. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. Philadelphia: Saunders, 1982:564–582.
(49) BLOT WJ. Lung cancer and occupational exposures. In: Mizell A, Correa P, eds. Lung cancer: Causes and prevention. Deerfield Beach, FL: Verlag Chemie, 1984:47–64.
(50) PETO R, DOLL R, BUCKLEY JD, et al. Can dietary beta-carotene materially reduce human cancer rates? Nature 1981; 290: 201–208.
(51) OOI WL, ELSTON RC, CHEN VW, et al. Increased familial risk for lung cancer. JNCI 1986; 76:217–222.
(52) GARLAND C, BARRETT-CONNER E, SUAREZ L, et al. Effects of passive smoking on ischemic heart disease mortality of nonsmokers. Am J Epidemiol 1985; 121:645–650.
(53) WEISS ST, TAGER IB, SCHENKER M, et al. The health effects of involuntary smoking. Am Rev Respir Dis 1983; 128:933–945.

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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING

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The purpose of this paper is to estimate the number of adult deaths per year in the United States from passive smoking. The epidemiological literature on passive smoking and adult mortality and cancer and heart morbidity is reviewed. Combined relative risks for lung cancer, cancers other than lung, and heart disease are calculated for each sex and disease category. These data along with estimates of nonsmoker death rates and populations exposed allow calculation of annual deaths in each category. Reduced relative risk and reduced exposure at older ages are taken into account as well as a correction for possible misclassification of smokers as nonsmokers and exposed nonsmokers as nonexposed. Altogether 46,000 deaths per year are calculated consisting of lung cancer (3000) other cancer (11,000) and heart disease (32,000). Reasons why such high estimates for other cancer and heart disease may be possible are explored. It is concluded that exposure to environmental tobacco smoke can have adverse long term health effects that are more serious than previously thought.

Introduction

Several attempts have been made to estimate U.S. adult mortality from passive smoking. For example, Repace and Lowrey (1985) estimated the lung cancer deaths to be about 5000 per year. Fong (1982) estimated total mortality at 10,000 to 50,000. Russell *et al.* (1986) estimated total U.S. mortality at more than 4000. The present estimate is based on epidemiological evidence currently available on lung cancer, cancers other than lung, and heart disease.

The Surgeon General of the United States (USSG, 1986) and the U.S. National Academy of Sciences (NRC, 1986) have issued reports stating that passive smoking can cause lung cancer. In the National Academy report the relative risks from the various lung cancer studies were combined into an overall relative risk using a procedure somewhat similar to that which is used in this work. The Academy report then projects that about 20% of the 12,000 U.S. lung cancer deaths per year among never smokers is due to passive smoking. This is reasonably close to the 3000 per year projected here for never smokers plus exsmokers. The methods used in the National Academy report are further detailed in Wald *et al.* (1986). Blot and Fraumeni (1986) have also presented an overview of studies of lung cancer and passive smoking. They use a method of combining the relative risks from various studies essentially identical to that used here. Thus, the procedure of combining relative risks from various passive smoking studies to obtain overall relative risks and tighter confidence intervals is now well established by authorities in the field. Also, the method used here to calculate annual deaths from the relative risks appears to be validated by the National Academy results for lung cancer. However, both the Surgeon General's task force and that of the National Academy felt that the data, as of 1986, on cancers other than lung and on heart disease were still too meager to allow calculation of reliable overall risks.

Since 1985 considerably new epidemiological information has become available, particularly on heart disease. This new information is reviewed and combined with the old data to calculate updated relative risks, overall confidence limits, and estimated annual U.S. deaths from passive smoking and the three main diseases, namely, lung cancer, cancers other than lung, and ischemic heart disease. The total particulate matter dose retained by passive smokers is too low to account for the health effects of passive smoking if one starts with the health effects exhibited by direct smokers and ratios down from the dose retained by them. Reasons why such a discrepancy might occur are explored.

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Methods

Studies to be considered in the analyses were obtained originally from the literature searches of the U.S. Office on Smoking and Health (OSH, 1979–85). More recently, studies have come to light primarily through personal contact with workers in the passive smoking field. Criteria for admitting data to the analysis are:

1. Studies on the association of passive smoking with adult mortality or morbidity from lung cancer, other cancer or ischemic heart disease were included. All cause data were not used because essentially no male data are available. The female data, if calculated, yield overall results that are in the same range as the results derived from the three main diseases (see Appendix B). Emphysema is not included because the nonsmoker death rate is so low that less than 1% of deaths from passive smoking would be predicted from this source (see Appendix B).
2. Retrospective studies should have controls.
3. Observations should be based on spouse exposure or on general exposure of more than 10 years duration. The diseases under study are known to have long induction periods, and it is assumed that most married people old enough to die of passive smoking would have been exposed 20 years or more.
4. Enough data should be available from the study to allow calculation of a weighting factor for combining the relative risks.

Two risk models were used and a third was considered. The primary model used combined relative risks from the various studies that pertained to a given sex and disease and assumed that the combined relative risk was constant with age, although variation with age of the underlying neversmoker death rate and the fraction of the population exposed were included. In the secondary risk model the combined relative risk was also allowed to vary with age. These models were suggested in part by the considerations in James Robins' Appendix D in the National Academy report (NRC, 1986). The third risk model was based on the rate difference between the death rates for exposed and nonexposed populations. A detailed analysis of this model for heart disease in women was carried out (see Appendix C). It was concluded that the relative risk models were much superior to the rate difference model when combining data across different cultures as is the case here where some of the studies are from the orient.

Wherever a study showed both a crude relative risk or odds ratio and an adjusted ratio, the adjusted ratio was used. To obtain a combined relative risk a method similar to that of Blot and Fraumeni (1986) was used. Case control studies were aggregated using Program 2 of Rothman and Boice (1982). Cohort studies were aggregated using Program 7. A combined relative risk for the two aggregates was obtained using:

$$R_{cb} = \exp \frac{w_{co} \ln R_{co} + w_{cc} \ln R_{cc}}{w_{co} + w_{cc}} \qquad (1)$$

where R_{cb}, R_{co}, and R_{cc} are the relative risks for the combined total, the cohort studies, and the case control studies, respectively, and w_{co} and w_{cc} are the weights for the cohort and case control studies, respectively, which are the inverse of the respective variances. Variance is taken as the square of the standard deviation which is equal to $\ln R/\chi$, so the weight, $w = (\chi/\ln R)^2$. The source of these equations is Rothman (1986). Confidence intervals were calculated from a combined $\chi = w^{1/2} \ln R_{cb}$. For some studies it was necessary to calculate a chi from the confidence limits in order to calculate a weight since no other data were available. These data were then combined with the rest using Eq. (1). Ages of death from 35 and up were used and should include essentially all adult deaths from passive smoking. In some studies morbidity relative risks were reported whereas our interest is in mortality. The morbidity relative risks were accepted as surrogates for mortality relative risks because, for cancer, the survival rates for exposed and nonexposed cases appeared to be similar while, for heart disease, incidence relative risks, if anything, are lower than mortality relative risks (Svendsen *et al.*, 1987).

The 1985 smoking status for U.S. residents in 5 year age increments was obtained from the National Center for Health Statistics. Nonsmokers were equated to never smokers plus exsmokers. The fractions of never smokers living with ever smokers (24% for males and 60% for females), all of whom were considered to be exposed, were obtained from controls of the U.S. based studies for all three diseases. These fractions were assumed to hold also for nonsmokers (never plus ex). The fractions of all nonsmokers exposed as nonsmokers living with nonsmokers, but still exposed at home or at work (37% for males and 16% for females), were obtained from Friedman *et al.* (1983). These fractions were assumed to hold for nonsmokers living with never smokers. By adding the two fractions the total nonsmoker exposure of 61% for males and 76% for females was obtained. These overall exposure fractions are known to be higher at younger ages and lower at older ages. The data of Friedman *et al.* (1983) were used to develop smoothed values of fraction exposed 10 years earlier (midpoint of a 20 year exposure) for each sex and 5 year age interval normalized to 61% for males and 76% for females. By multiplying each population element by each fraction exposed element, the exposed population by sex and 5 year age interval could be determined.

Death rates for never smokers for lung cancer by sex and 5 year intervals were drawn from Garfinkel (1981)

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and smoothed using a semi-log plot against age. For cancers other than lung for females a semi-log plot of 1984 age specific death rates for ages 35+ was developed for malignant neoplasms less malignant respiratory neoplasms from the data of the National Center for Health Statistics (1986). Then, a parallel plot was developed using as reference points the neversmoker data of Hammond (1966) for ages 45–64 and 65–79 to yield neversmoker rates for ages 35+ for each 5 year age interval. For heart disease never smoker death rates by sex and 5 year age intervals for 1963 were developed from the appendix tables in Hammond (1966). These were reduced to 1984 equivalent rates (with the reduction factors corrected for the effects of smoking) by a technique similar to that used by the U.S. Office of Technology Assessment (OTA, 1985). Semi-log graphs were used to estimate never smoker death rates by 5 year age intervals for the entire age range (see Appendix A, Table A3).

The excess death rate for never smokers for passive smoking (D_{ps}) for each sex, disease and 5 year age range was calculated from the never smoker death rates (D_{ns}) using the formula:

$$D_{ps} = D_{ns}(R - 1)/(F_p(R - 1) + 1) \qquad (2)$$

where F_p is the fraction of the population that is exposed and R is the combined relative risk. This excess death rate was assumed to apply to all nonsmokers. Deaths were then calculated by multiplying the passive smoking excess death rate by the exposed population for each sex and 5 year age interval, and summed. For those calculations where the relative risk was assumed to have varied with age, the excess death rates for passive smoking were recalculated from the age specific relative risks for each 5 year age interval. Additional calculations were carried out to show the effects of bias including those from misclassification of smokers as nonsmokers and exposed nonsmokers as unexposed, using a method similar to that of Wald *et al.* (1986).

Results

Relative risks

The results for passive smoking relative risk for females for lung cancer are shown in Table 1. The three cohort studies are listed first and show a combined relative risk for all exposures including exposures to exsmokers of 1.34. At the time the analysis was made there were fourteen acceptable case control studies with a combined relative risk of 1.50. The overall combined relative risk, based on 1,174 cases, is 1.44 with 95% confidence limits of 1.3–1.7. The male lung cancer observed relative risks are shown in Table 2. There are now nine studies with 144 total cases. The overall combined relative risk is 2.1 with 95% confidence limits of 1.3–3.2. Data excluded from Tables 1 and 2 along with the reasons were the following: Chan *et al.* (1979), current exposure only; Knoth *et al.* (1983), no controls; Kabat and Wynder (1984) nonspouse data, current exposure only; Buffler *et al.* (1984), 0–32 year data, not a minimum of 10 years exposure. A paper by Dalager *et al.* (1986) describes a pooling of data from Correa *et al.* (1983), Buffler *et al.* (1984) and a study of males in New Jersey. They observed an adjusted odds ratio for spouse exposure of 1.47, but since Correa *et al.* (1983), and Buffler *et al.* (1984), were already included in Tables 1 and 2 and since the New Jersey data were not available separately, it was decided to omit the Dalager *et al.* (1986) study from this analysis. Also, available were abstracts of two recent papers, Geng *et al.* (1987) from China with a relative risk of 2.2 and Inoue and Hirayama (1987) from Japan with a relative risk of 2.3, both for females. Also W. K. Lam (1985) in a thesis from the University of Hong Kong that is quoted in Lam *et al.* (1987) found a relative risk of 2.0 for adenocarcinoma among females. These inputs arrived too late to be included in the analysis.

The data of Hirayama (1984a) on female lung cancer are sufficiently detailed to indicate a declining relative risk with age from 1.87 at approximately age 50 to 1.43 at approximately age 75. These data were used to develop a second death calculation assuming a declining relative risk, but still normalized to 1.44. However, Hirayama's data show no such decline in passive smoking relative risk with age for males. Instead, the trend appears to rise with age, so no secondary calculation was made.

There are now five studies relating passive smoking to total cancer or cancer other than lung in females. The individual and combined relative risks for females are shown in Table 3. The total combined relative risk is 1.16. The total cases, 2,933, are two and one-half times the total cases for female lung cancer (Table 1) although 2,505 are concentrated in the large Hirayama (1984a) study. This is a large data base. The total combined chi square is 11 compared to 27 for female lung cancer.

The two largest of the female studies, Hirayama (1984a) and Sandler *et al.* (1985), cover different age of death ranges. Hirayama covers 50 to 80+ while Sandler *et al.* cover <30 to 59. The two studies taken together would indicate a rather sharp decline in relative risk with age from about 3.5 at age 40 to about 1.04 at age 80. The high relative risks at the younger ages may be due to premenopausal breast cancer (see Sandler *et al.*, 1986). Two calculations of U.S. female deaths from passive smoking and other cancers were made, one using the 1.16 relative risk from Table 3 at all ages and one using the declining relative risks.

Gillis *et al.* (1984), Sandler *et al.* (1985), and Reynolds (private communication) also report on other can-

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Table 1. Female relative risks for lung cancer from passive smoking

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95 % C.L.	Mantel Trend 1-tail p
Cohort Studies:							
Hirayama (1984a)	Japan	200	1.9	0.002	1.6	1.1–2.2	0.002
Garfinkel (1981)	United States	153	1.1	—	1.2	0.8–1.6	—
Gillis *et al.* (1984)	Scotland	8	—	—	1.1	0.2–5.6	
Combined Cohort		361			1.34	1.1–1.7	
Case Control Studies:							
Trichopoulos *et al.* (1983)	Greece	77	2.6	0.19	2.1	1.2–3.6	0.005
Correa *et al.* (1983)	Louisiana	22	3.5	0.02	2.1	0.8–5.2	—
Buffler *et al.* (1984)	Texas	27[a]	—	—	0.9	0.4–2.3	—
Kabat and Wynder (1984)	United States	24	—	—	0.8	0.3–2.5	—
Sandler *et al.* (1985)	North Carolina	2	—	—	inf	—	—
Garfinkel *et al.* (1985)	United States	116	2.0	0.05	1.3	0.8–1.9	0.025
Wu *et al.* (1985)	California	28[a]	—	—	1.2	0.5–3.3	—
Lee *et al.* (1986)	United Kingdom	32	—	—	1.0	0.4–2.7	—
Akiba *et al.* (1986)	Japan	94	2.1	—	1.5	0.9–2.6	0.06
Koo *et al.* (1987)	Hong Kong	86	1.2	—	1.6	0.9–3.1	—
Pershagen *et al.* (1987)	Sweden	67	3.2	—	1.2	0.7–2.1	0.12
Humble *et al.* (1987)	New Mexico	20	1.2	—	2.3	0.9–6.6	—
Brownson *et al.* (1987)	Colorado	19	—	—	1.7	0.4–3.0	—
Lam *et al.* (1987)	Hong Kong	199	—	—	1.65	1.2–2.4	
Combined Case Control		813			1.50		1.3–1.8
Combined Cohort and C/C		1174			1.44	1.26–1.66	

[a] Private communication.
[b] From Blot and Fraumeni (1986).

cer in males. The relative risks were 0.6, 1.5 and near unity, respectively. The number of cases in each study is very small with no statistical significance. Therefore, it was decided to use a neutral relative risk of 1.0 for males for cancer other than lung until more data become available.

There are now six studies of passive smoking and heart disease in females. The individual and combined relative risks are shown in Table 4. Studies new since 1985 are Lee *et al.* (1986), Martin *et al.* (1986a) and the important, large Helsing *et al.* (1988) paper from Maryland. The overall combined relative risk based on 1,622 cases is 1.23 with 95% confidence limits of 1.11 to 1.36 and a combined chi square of 16. Helsing *et al.* (1988) and Martin *et al.* (1986a) provide data for younger women and indicate high relative risks (average 2.45)

Table 2. Male relative risks for lung cancer from passive smoking.

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95 % C.L.	Mantel Trend 1-tail p
Cohort Studies							
Hirayama (1984a)	Japan	64	2.3	0.16	2.25	1.11 - 4.9	0.023
Gillis *et al.* (1984)	Scotland	6	—	—	3.3	0.7 -16.5	—
Combined Cohort		70			2.5	1.2 - 5.0	
Case Control Studies:							
Correa *et al.* (1983)	Louisiana	8	—	—	2.0	0.4 -10	—
Buffler *et al.* (1984)	Texas	8[a]	—	—	1.6	0.3 - 8.1	—
Kabat and Wynder (1984)	United States	12	—	—	1.0	0.3 - 3.2	—
Lee *et al.* (1986)	United Kingdom	15	—	—	1.3	0.4 - 4.6	—
Akiba *et al.* (1986)	Japan	19	—	—	1.8	0.5 - 5.6	—
Humble *et al.* (1987)[a]	New Mexico	8	—	—	4.2	1.0 -16.8	—
Brownson *et al.* (1987)[a]	Colorado	4			2.7	0.2 -31	—
Combined Case Control		74			1.8	1.0 - 3.3	—
Combined Cohort and C/C		144			2.1	1.3 - 3.2	

[a] Private Communication.

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Table 3. Female relative risks for cancer other than lung from passive smoking

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95 % C.L.	Mantel Trend 1-tail p
Cohort Studies:							
Hirayama (1984a)[a]	Japan	2505	1.16	0.01	1.11	1.0 -1.2	0.05
Gillis *et al.* (1984)	Scotland	43	—	—	1.2	0.6 -2.5	—
Reynolds *et al.* (1987)	California	70[b]	—	—	1.7	1.1 -2.7	—
Combined Cohort		2618			1.13	1.03–1.24	—
Case Control Studies:							
Miller (1984)[c]	Pennsylvania	84	—	—	1.25	0.7 -2.3	—
Sandler *et al.* (1985)	North Carolina	231	—	—	2.0	1.3 -2.9	—
Combined Case Control		315			1.7	1.2 -2.45	
Combined Cohort and C/C		2933			1.16	1.06–1.27	

[a]Obtained by subtracting data for lung cancer from data for all sites.
[b]Provided by Dr. Reynolds.
[c]Age adjusted Mantel-Haenszel values for nonemployed wives.

for ages up to about 50. At higher ages there is no trend with an average relative risk of 1.17 holding out to age 84.

For male heart disease and passive smoking there are now four studies (see Table 4). The two new ones are Lee *et al.* (1986) and Helsing *et al.* (1988). The result of Svendsen *et al.* (1987) is shown for information, but is not used in calculating the combined relative risk because it pertains to a high risk group. The combined relative risk based on 443 cases is 1.31 with 95% confidence limits of 1.1 to 1.6 and a combined chi square of 9. The results are remarkably uniform. As in the female data the relative risk is high at the younger ages, about 2.9, but declines to a nontrend average of 1.28 which extends from age 55 out to the older ages. Svendsen *et al.* (1987) show that there was very little difference between never smoking men married to nonsmokers and those married to smokers in the major coronary risk factors such as baseline blood pressure, total cholesterol, and LDL cholesterol. This work was reported in more detail in Martin *et al.* (1986b). Small differences were found in weight (195 vs. 190 if wives were smokers) and drinks per week (10 vs. 8 if wives were smokers). On the other hand, Garland *et al.* (1985)

Table 4. Relative risks for heart disease from passive smoking.

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95 % C.L.	Mantel Trend 1-tail p
Females							
Cohort Studies:							
Hirayama (1984b)	Japan	494	1.3	0.038	1.16	0.9– 1.4	0.02
Gillis *et al.* (1984)	Scotland	21	—	—	3.6	0.9–13.8	—
Garland *et al.* (1985)	California	19	—	—	3.5	0.9–13.6	—
Helsing *et al.* (1988)	Maryland	988	1.27	—	1.24	1.1– 1.4	0.005[a]
Combined Cohort		1522			1.23	1.1– 1.4	
Case Control Studies:							
Lee *et al.* (1986)	United Kingdom	77	—	—	0.9	0.7– 1.3	—
Martin *et al.* (1986a)	Utah	23	—	—	2.6	1.2– 5.7	—
Combined Case Control		100			1.29	0.8– 2.0	
Combined Cohort and C/C		1622			1.23	1.1– 1.4	
Males							
Cohort Studies:							
Gillis *et al.* (1984)	Scotland	32	—	—	1.30	0.7– 2.6	—
Lee *et al.* (1986)	United Kingdom	41	—	—	1.24	0.5– 2.6	—
Helsing *et al.* (1988)	Maryland	370	—	—	1.31	1.1– 1.6	—
Combined Cohort		443			1.31	1.1– 1.6	—
Svendsen *et al.* (1987)[b]	United States	13	—	—	2.2	0.7– 6.9	—

[a]Based on Cochran chi-square of 9.2.
[b]MRFIT cohort of high risk individuals, included for information only.

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found that never smoking women married to smokers had slightly lower weight, slightly lower blood pressure, and slightly higher cholesterol, all nonsignificantly different, versus never smoking women married to never smokers. All of these authors conclude that the increased passive smoking risks they observed cannot be ascribed to differences in the major coronary risk factors between passively exposed and nonexposed never smokers.

It is impressive that the relative risks for heart disease from passive smoking rise in an orderly manner from the lowest risk group, Japanese women at 1.16, through American women at 1.27, and American men at 1.31, to high risk American men at 2.2.

A correction for misclassification was attempted for all three disease categories. Following Wald *et al.* (1986), and presuming that the passive smoking studies were done somewhat more carefully than the general questionnaire studies they cite, it was assumed that 5% of ever smokers were misclassified as never smokers. Along with Wald *et al.* (1986) we assumed that the nonexposed nonsmokers were actually exposed to 1/3 the extent of the exposed nonsmokers except that for Greece, Japan, and Hong Kong, where less than 30% of women had ever smoked, the correction for nonexposed female nonsmokers was omitted. It is believed that older, nonsmoking women in Greece and Japan, and probably in Hong Kong also, because of their social habits, were exposed to relatively little tobacco smoke beyond that of their husband's. Since most of the misclassified smokers were found to be light smokers or longstanding exsmokers, reduced relative risks for the misclassified ever smokers were calculated, as noted in Appendix A. The modified passive smoking relative risks are shown in Table 5. The false relative risks due to smoker misclassification are somewhat lower than calculated earlier by Wells (1986) because of the assumption of light smokers and long term exsmokers among those misclassified, following Wald *et al.* (1986), and the use of a more accurate formula. In general, the misclassification of smokers has a large negative effect on male relative risk which is more or less offset by the positive effect of exposure of the "nonexposed." For females the smoker misclassification effect is small to negligible, but because the relative risks are smaller and no correction was made to "eastern" data (Japan, Greece, and Hong Kong), the positive effects of exposure of "nonexposed" are also smaller.

Calculation of Deaths

The details for the calculation of female lung cancer deaths from the relative risks, both constant and declining, are shown in Table 6 as an example. Similar calculations were made for the other disease and sex categories and are shown in Appendix A. The results of all of the calculations are summarized in Table 7. These results are restated per million total population in Table 8. Where the relative risk appears to decline with age and where neversmoker death rates at the younger ages are low, as in female heart disease and lung cancer, there is a reduction in mortality calculated by using the age specific relative risks. Otherwise, the higher exposed population at the younger ages outweighs the higher death rate at older ages and total mortality is increased. In terms of total deaths the effects of using age specific relative risks tend to cancel out. The total deaths, before adjustment for misclassification, for both males and females are about 19,500 for a total for both sexes of about 39,000.

The effects of misclassification on total deaths are substantial, raising the total to 53,000. Most of this increase is in heart disease where the numbers are large and the effects of smoker misclassification, although not necessarily small, are still heavily outweighed by the partial exposure of the "nonexposed."

To be conservative a best estimate for passive smok-

Table 5. Passive smoking relative risks modified for misclassification.

	Lung Cancer	Other Cancer	Heart Disease
Females			
1. Combined relative risk.	1.44	1.16	1.23
2. False relative risk due to projected 5% smoker misclassification.	1.01	1.002	1.01
3. Combined relative risk corrected for smoker misclassification. (1) ÷ (2).	1.43	1.16	1.22
4. (3) corrected for exposure of "nonexposed" at 1/3 that of exposed.	1.48	1.21	1.32
Males			
1. Combined relative risk.	2.1	1.0*	1.31
2. False relative risk due to projected 5% smoker misclassification.	1.3	—	1.11
3. Combined relative risk corrected for smoker misclassification. (1) ÷ (2).	1.6	—	1.17
4. (3) corrected for exposure of "nonexposed" at 1/3 that of exposed.	2.4	—	1.29

*Assumed value for lack of better data.

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Table 6. Annual U. S. female lung cancer deaths from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000	Nonsmoker Population 1000's	Fraction Exposed	Exposed Population 1000's	Relative Risk Constant at 1.44		Relative Risk Declining	
					Excess Death Rate	Deaths	RR	Deaths
35–39	1.6	6150	0.94	5781	0.50	29	1.70	39
40–44	2.4	4622	0.92	4252	0.75	32	1.69	43
45–49	3.6	3846	0.89	3423	1.14	39	1.68	52
50–54	5.3	3856	0.87	3355	1.69	57	1.62	72
55–59	7.8	4161	0.84	3495	2.51	88	1.56	104
60–64	11.0	4192	0.77	3228	3.62	117	1.49	126
65–69	16.6	4160	0.70	2912	5.55	162	1.43	159
70–74	23.5	3441	0.59	2030	8.21	167	1.36	142
75–79	34	3004	0.49	1472	12.3	181	1.29	127
80–84	46	1886	0.29	547	18.0	98	1.18	43
85–	52	1003	0.10	100	21.9	22	1.08	4
Totals	13.0	40291	0.76	30595	3.0	992	—	911

ing deaths might be 46,000, half way between the 39,000 calculated directly from the relative risks and the 53,000 calculated using the modified relative risks. By disease the total would consist of 3,000 lung cancer, 11,000 other cancer, and 32,000 heart disease. For each million of total population the deaths by disease would be 13 for lung cancer, 46 for other cancers, and 134 for heart disease. These numbers may be useful for populations similar to that of the United States in terms of proportions of never smokers, exsmokers, and smokers, and in terms of the proportion of the population that is less than 35 relative to that over 35. For other populations the per million numbers are best not used, but the methodology can be used. That cancer other than lung and heart disease are legitimate contributors to deaths from passive smoking is supported in Hirayama, (1984a,b) in his large prospective study. He found significantly elevated risks for all three diseases, and his result for lung cancer is now believed to be valid, (USSG 1986; NRC, 1986). It is difficult to believe that his lung cancer result is valid while the other two are not.

Discussion

The cancer sites for passive smoking appear to differ somewhat from those for direct smoking. Using information on specific cancer sites from Dr. Hirayama (private communication) it appears that cancers common to both types of smoking are lung, liver, cervix, nasal sinus, and leukemia. Some of these cancers are only weakly associated with direct smoking. Cancers associated to some degree with direct smoking, but absent in passive smoking are buccal cavity, pharynx, larynx, esophagus, stomach (Hirayama, 1984a), urinary bladder (Kabat *et al.*, 1986), kidney and pancreas. Cancers related to passive smoking, but absent in direct smoking are brain (Hirayama, 1984a), endocrine glands (Sandler *et al.*, 1985), lymphoma and breast (Sandler *et al.*, 1985, 1986; Hirayama, private communication). The first three are significant at the 95% level. The combined breast relative risk of 1.4 is significant at only 88%. Higher relative risks for these four sites might be found for direct smoking if epidemiologists used nonpassively

Table 7. Summary: U.S. annual deaths from passive smoking.

	Lung Cancer	Other Cancer	Heart Disease	Total
Females:				
1. Constant combined relative risk.	992	8599	9768	19359
2. Relative risk declining with age.	911	11165	7602	19678
3. (1) corrected for misclassification.	1232	12280	14995	28507
Males:				
1. Constant combined relative risk.	1606	0	17335	18941
2. Relative risk declining with age.	1606	0	18164	19770
3. (1) corrected for misclassification.	2499	0	22467	24966
Totals for both sexes:				
1. Constant combined relative risk.	2598	8599	27103	38300
2. Relative risk declining with age.	2517	11165	25766	39448
3. (1) corrected for misclassification.	3731	12280	37462	53473
Best current estimate, both sexes (rounded).	3000	11000	32000	46000

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Table 8. Summary: Deaths per million population in U.S. from passive smoking. (based on 23,000,000 U.S. population in 1985).

	Lung Cancer	Other Cancer	Heart Disease	Total
Females:				
1. Constant combined relative risk	4.15	35.98	40.87	81.00
2. Relative risk declining with age	3.81	46.71	31.81	82.33
3. (1) corrected for misclassification	5.15	51.38	62.74	119.27
Males:				
1. Constant combined relative risk	6.72	0	72.53	79.25
2. Relative risk declining with age	6.72	0	76.00	82.72
3. (1) corrected for misclassification	10.46	0	94.00	104.46
Totals for both sexes:				
1. Constant combined relative risk	10.87	35.98	113.40	160.25
2. Relative risk declining with age	10.53	46.71	107.81	165.05
3. (1) corrected for misclassification	15.61	51.38	156.74	223.73
Best current estimate, both sexes (rounded)	13	46	134	193

exposed never smokers as the referrent category rather than all never smokers as is usually done. Another difference between passive smoking and direct smoking is that the ratio of lung cancer deaths to deaths from other cancer for females or from heart disease for both sexes is much lower in passive smoking than in direct smoking.

These differences in mortality effects are probably real and reflect differences in chemistry and physics between direct smoking and passive smoking. Environmental tobacco smoke is generated in the burning tip of the cigarette at a lower temperature than direct smoke and therefore contains higher proportions of complicated organic compounds that tend to be carcinogenic (Brunnemann *et al.*, 1978). More importantly, (see Appendix D) the mainstream smoke, although generated at a particle size of about 0.7 μm, is very concentrated and appears to agglomerate into larger particles. Deposition rates are high, about 80%. Deposition occurs primarily in the mouth or in the larger airways of the lung where the particles are cleared relatively quickly into the mouth. This material is then swallowed. Some of it may be eliminated and produce no health effects at all or it may cause the digestive type cancers observed. Only a portion of mainstream smoke appears to remain as small particles that can penetrate deeply into the alveolar region. Environmental tobacco smoke, on the other hand, is very dilute, with a mass median diameter of about 0.4 μm. Particles in this size range have very low deposition rates, on the order of 10%, but what does deposit does so deep in the alveolar region of the lung where clearance times are longer. Black and Pritchard (1984) estimate that cigarette tar has a 17 hour half-time rate of clearance from the alveolar region, much longer than clearance times from the ciliated parts of the lung, but much shorter than for inert particles. This means that smoke particles are very likely dissolving in the fluids in the alveolar region and are being cleared into the blood and lymph systems for circulation throughout the body.

In summary, there are two types of smoking: (a) large particle smoking, or its equivalent, which is the major component of direct smoking, which results in massive deposition in the mouth and larger airways of the lung, rapid clearance, cancers of the mouth, central lung and digestive system, and possibly heart disease, and (b) small particle smoking, which is a minor component of direct smoking, but the entirety of passive smoking, and which results in low doses deep in the lung, slow clearance, some lung cancer, but primarily other cancers and adverse heart effects.

These differences in chemistry and physics also explain, at least in part, the rather high mortality observed for passive smoking relative to the deposited dose of particulate. Smoke retention by a passive smoker is only about 1/400 that retained by a direct smoker in a 16 hour day (0.64 mg for the passive smoker per USSG (1986, p. 196) and 240 mg for the direct smoker assuming twenty 15 mg tar cigarettes and 80% retention). In comparison, the ratio of lung cancer death rates is about 1/35. For cancers other than lung in females the ratio is about 1/7, for heart disease in females about 1/14 and for heart disease in males about 1/3. Preliminary calculations which are shown in Appendix D indicate that the smoke retained deep in the alveolar region may have a dose ratio higher than 1/400, perhaps as high as 1/60. It may be that carcinogenic material that solubilizes and clears from the alveoli into the blood may cause not only some of the cancers other than lung that are observed in passive smoking, but also some of the heart disease from passive as well as direct smoking. The hypothesis of Benditt and Benditt (1973) that arterial plaques are caused by DNA-modifying agents is receiving increasing support. See, for example, the recent work of Penn *et al.* (1986) on cell transforming capability of human atherosclerotic plaque DNA and the earlier work of Albert *et al.* (1977) and Penn *et al.* (1981) on the formation of arterial plaques in cockerels with dimethylbenz(α)anthracene and benzo(α)pyrene.

Another possible factor that might help explain the disparate mortality effects versus dose is the level of disease susceptability in passive smokers versus direct

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smokers. The median age for passive smoking death from lung cancer for males is 66 and the deaths constitute 0.006% per year of the exposed population. The first 0.006% of male smokers have died of lung cancer by age 46 at which age the lung cancer death rate is doubling every four years. At age 66 the smoker lung cancer death rate is doubling about every 13 years. In other words, in passive smoking deaths we are dealing with only the very most susceptible people, whereas in direct smoking most of the victims are much nearer average susceptibility. Similar considerations apply to the other diseases here discussed.

A question often raised is that direct smokers are also passive smokers, so why do they not get the passive smoking related cancers. We have already pointed out that the use of nonexposed never smokers as the referrent category for smoker relative risk would increase the apparent risk for smokers. Another possible explanation is the probability of competing risks. Most of the highly susceptible direct smokers would have died in their forties or fifties from smoking related disease and would not be available to die of passive smoking related disease in their sixties or seventies.

The passive smoking mortality calculated in this study, namely, 46,000, may be low. Repace and Lowrey (1985) calculate lung cancer deaths from passive smoking at 4,665, or about 50% higher than our estimate, primarily because of postulated intense exposure at the workplace, a factor not taken into account in this study since the relative risks are based largely on home exposure. If Repace and Lowrey are correct, the higher exposure would lead to corresponding increases in deaths from heart disease and other cancer. Also, only ischemic heart disease is considered here. As the all cause data in Appendix B indicate, other cardiovascular diseases and diabetes may be sensitive to environmental tobacco smoke and may increase the total deaths.

The new epidemiological studies on passive smoking support the earlier ones and indicate that not only lung cancer, but other cancer and heart disease are serious problems. In fact, lung cancer appears to be only the tip of the iceberg. To be on the safe side public health policy should be to protect nonsmokers from environmental tobacco smoke.

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References

Akiba, S., Kato, H., and Blot, W. J. (1986) Passive smoking and lung cancer among Japanese women. *Cancer Res* **46**, 4804–4807.

Albert, R. D., Vanderlaan, M., Burns, F., and Nishizumi, M. (1977) *Cancer Res* **37**, 2232–2235.

Balin, B. J. Broadwell, R. D., Salcman, M., El-Kalling, M. (1986) Avenues for entry of peripherally administered protein to the central nervous system in mouse, rat, and squirrel monkey. *J. Comp Neurol* **251**, 260–280.

Benditt, E. P. and Benditt, J. M. (1973) Evidence for a monoclonal origin of human atherosclerotic plaques. *Proc Natl Acad Sci* **70**, 1753–1756.

Black, A. and Pritchard, J. N. (1984) A comparison of the regional deposition and short term clearance of tar particulate material from cigarette smoke, with that of 2.5 μm polystyrene microspheres. *Aerosol Sci* **15**, 224–227.

Blot, W. J. and Fraumeni, J. F. (1986) Passive smoking and lung cancer. *J Nat Cancer Inst* **77**, 993–1000.

Brownson, R. C., Reif, J. S., Keefe, T. J., Ferguson, S. W., and Pritzl, J. A. (1987) Risk factors for adenocarcinoma of the lung. *Am J Epidemiol* **125**, 25–34.

Brunnemann, K. D., Adams, J. D., Ho, D. P. S., and Hoffmann, D. (1978) The influences of tobacco smoke on indoor atmospheres II. Volatile and tobacco specific nitrosamines in main and sidestream smoke and their contribution to indoor pollution. in *Proceedings, 4th Joint Conference on Sensing of Environmental Pollutants*, New Orleans, Louisiana, 1977. American Chemical Society, Washington, D.C., 876–880.

Buffler, P. A., Pickle, L. W., Mason, T. J., and Contant, C. (1984) The causes of lung cancer in Texas. in *Lung cancer: Causes and prevention*, M. Mizell and P. Correa, eds., pp. 83–99. Verlag Chemie International, New York.

Chan, W. C., Colbourne, M. J., Fung, S. C., and Ho, H. C. (1979) Bronchial cancer in Hong Kong 1976–1977. *Br J Cancer* **39**, 182–192. Chan, W. C. and Fung, S. C. (1982) Lung cancer in nonsmokers in Hong Kong, in *Cancer campaign, Vol. 6. Cancer Epidemiology*, E. Grundmann, ed., pp. 199–202. Gustav Fischer Verlag, Stuttgart, New York.

Correa, P., Pickle, L. W., Fontham, E., Lin, Y., and Haenszel, W. (1983) Passive smoking and lung cancer. *Lancet* **ii**, 595–597.

Dalager, N. A., Pickle, L. W., Mason, T. J., Correa, P., Fontham, E., Stemhagen, A., *et al.* (1986) The relation of passive smoking to lung cancer. *Cancer Res* **46**, 4808–4811.

Fong, P. (1982) The hazard of cigarette smoke to nonsmokers. *J. Biol. Phys* **10**, 65–73.

Freidman, G. D., Petitti, D. B., and Bawol, R. D. (1983) Prevalence and correlates of passive smoking. *Am J Public Health* **73**, 401–405.

Fuchs, N. A. (1964) *The Mechanics of Aerosols*, pp. 46–49. Macmillan, New York.

Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J Nat Cancer Inst* **66**, 1061–1066.

Garfinkel, L., Auerbach, O., and Joubert, L. (1985). Involuntary smoking and lung cancer: A case control study. *J Nat Cancer Inst* **75**, 463–469.

Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M. H., and Wingard, D. L. (1985) Effects of passive smoking on ischemic heart disease mortality of nonsmokers. *Am J Epidemiol* **121**, 645–650.

Geng, G. Y., Liang, Z. H., Zhang, A. Y., and Wu, G. L. (1987, November) On the relationship between cigarette smoking and female lung cancer. Paper presented at the 6th World Conference on Smoking and Health, Tokyo.

Gerrity, T. R., Lee, P. S., Hass, F. J., Marinelli, A., Werner, P., and Lourenço, R. V. (1979) Calculated deposition of inhaled particles in the airway generations of normal subjects. *J Appl. Physiol: Respirat Environ Exercise Physiol* **47**, 867–873.

Gillis, C. R., Hole, D. J., Hawthorne, V. M., and Boyle, P. (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur J Resp Dis* **65**, (supplement No. 133), 121–126.

Hammond, C. (1966) Smoking in relation to the death rates of one million men and women. in *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*, W. Haenszel, ed., pp. 127–204. U.S. Public Health Service, Bethesda, MD, (National Cancer Institute Monograph 19).

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Helsing, K. J., Sandler, D. P., Comstock, G. W., and Chee, E. (1988) Heart disease mortality in nonsmokers living with smokers. *Am J Epidemiol* 127, 915–922.

Heyder, J. (1984) Studies of particle deposition and clearance in humans. in *Problems of Inhalatory Toxicity Studies* P. Grosdanoff, *et al.*, eds., pp. 155–180. MMV-Medizin-Verlag, Munich.

Hiller, F. C., McCusker, K. T., Mazumder, M. M. K., Wilson, J. D., and Bone, R. C. (1982) Deposition of sidestream cigarette smoke in the human respiratory tract, *Am Rev Resp Dis* 125, 406–408.

Hirayama, T. (1984a) Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan, *Prev Med* 13, 680–690.

Hirayama, T. (1984b) Lung cancer in Japan: Effects of nutrition and passive smoking, in *Lung cancer: Causes and prevention*, M. Mizell, P. Correa, eds., pp. 175–195. Verlag Chemie International, New York.

Hirayama, T. (1987) Passive smoking and cancer: An epidemiological review, in *Gann Monograph on Cancer Research* 33, Japan Scientific Societies Press, Tokyo, pp. 127–135.

Humble, C. G., Samet, J. M., and Pathak, D. R. (1987) Marriage to a smoker and lung cancer risk, *Am J Pub Health* 77, 598–602.

Inoue, R. and Hirayama, T. (1987, November) Passive smoking and lung cancer in women. Paper presented at the 6th World Conference on Smoking and Health, Tokyo.

Kabat, G. C. and Wynder, E. L. (1984) Lung cancer in nonsmokers, *Cancer* 53, 1214–1221.

Kabat, G. C., Diech, G. S., and Wynder, E. L. (1986) Bladder cancer in nonsmokers, *Cancer* 57, 362–367.

Kalandidi, A., Trichopoulos, D., Hatzakis, A., Tzannes, S., and Saracci, R. (1987) Passive smoking and chronic obstructive lung disease, *Lancet* II, 1325–1326.

Knoth, A., Bohn, H., and Schmidt, F. (1983) Passivrauchen als Lungenkrebs-Ursache bei Nichtraucherinnen, *Medizinische Klinik* 78, 66–69.

Koo, L. C., Ho, J. H. C., Saw, D., and Ho, C. (1987) Measurements of passive smoking and estimates of lung cancer risk among nonsmoking Chinese females, *Int J Cancer* 39, 162–169.

Lam, T. H., Kung, I. T. M., Wong, C. M., Lam, W. K., Kleevens, J. W. L., Saw, D., *et al.* (1987) Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women, *Br J Cancer* 56, 673–678.

Lam, W. K. (1985) A clinical and epidemiological study of carcinoma of lung cancer in Hong Kong, M.D. thesis, University of Hong Kong, Hong Kong.

Lee, P. N., Chamberlain, J., and Alderson, M. R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases, *Br J Cancer* 54, 97–105.

Martin, M. J., Hunt, S. C., and Williams, R. R. (1986a, October) Increased incidence of heart attacks in nonsmoking women married to smokers. Paper presented at annual meeting of American Public Health Association.

Martin, M. J., Svendsen, K. H., and Kuller, L. H. (1986b, March) Nonsmoking men married to smokers are similar to nonsmoking men married to nonsmokers. Paper presented at the 7th Annual Meeting, Society for Behavioral Medicine.

Melandri, C., Tarroni, G., Prodi, V., DeZaiacomo, T., Formignani, M., and Lombardi, C. C. (1983) Deposition of charged particles in the human airways, *J Aerosol Sci* 14, 657–669.

Miller, G.H. (1984) Cancer, passive smoking and non-employed and employed wives, *West J Med* 140, 632–635.

Mitchell, R. I. (1962) Controlled measurement of smoke particle retention in the respiratory tract, *Am Rev Respir Dis* 85, 526–533.

National Center for Health Statistics (1986) Health United States 1986, U.S. Dept. of Health and Human Services, Public Health Service, Hyattsville, MD, 106–109.

National Research Council (1986) Environmental tobacco smoke, measuring exposures and assessing health effects, National Academy Press, Washington, D.C.

Office of Technology Assessment (1985) Smoking related deaths and financial costs, Office of Technology Assessment, U.S. Congress, Washington, D.C. Office on Smoking and Health (1979–85) Bibliography on smoking and health, U.S. Public Health Service, Rockville, MD, and Smoking and Health Bulletins after 1985.

Penn, A., Batastini, G., Solomon, J., Burns, F., and Albert, R. E. (1981) *Cancer Res* 41, 588–592.

Penn, A., Garte, S. J., Warren, L., Nesta, D., and Mindich, B. (1986) Transforming gene in human atherosclerotic plaque DNA, *Proc Nat Acad Sci* 83, 7951–7955.

Pershagen, G., Hrubec, Z., and Svensson, C. (1987) Passive smoking and lung cancer in Swedish women, *Am J Epidemiol* 125, 17–24.

Repace, J. L. and Lowrey, A. H. (1985) A quantitative estimate of nonsmokers' lung cancer risk from passive smoking, *Environ Int* 11, 3–22.

Reynolds, P., Kaplan, G. A., and Cohen, R. D. (1987, June) Passive smoking and cancer incidence: prospective evidence from the Alameda County study. Paper presented at the Society for Epidemiologic Research, Amherst, Massachusetts.

Rothman, K. J. and Boice, J. D. (1982) *Epidemiologic Analysis with a Programmable Calculator*, pp. 5–17. Epidemiology Resources, Chesnut Hill, Massachusetts.

Rothman, K. J. (1986) *Modern Epidemiology*, pp. 139–147, 184–190. Little, Brown, Boston.

Russell, M. A. H., Jarvis, M. J., and West, R. J. (1986) Use of urinary nicotine concentrations to estimate exposure and mortality from passive smoking in non-smokers, *Br J Addiction* 81, 317–323.

Sandler, D. P., Everson, R. B., and Wilcox, A. J. (1985) Passive smoking in adulthood and cancer risk, *Am J Epidemiol* 121, 37–48.

Sandler, D. P., Everson, R. B., and Wilcox, A. J. (1986) Cigarette smoking and breast cancer, *Am J Epidemiol* 123, 370–371.

Stöber, W. (1984) Lung dynamics and uptake of smoke constituents by nonsmokers—a survey, *Prev Med* 13, 589–601.

Svendsen, K. H., Kuller, L. H., and Neaton, J. D. (1987) Effects of passive smoking in the multiple risk factor intervention trial, *Am J Epidemiol* 126, 783–795.

Trichopoulos, D., Kalandidi, A., and Sparros, L. (1983) Lung cancer and passive smoking: Conclusion of the Greek study, *Lancet* II, 677–678.

U.S. Surgeon General (1986) The health consequences of involuntary smoking, a report of the Surgeon General, DHHS (CDC) 87-8398, U.S. Public Health Service, Rockville, Maryland.

Vandenbroucke, J. P., Verheesen, J. H. H., deBruin, A., Mauritz, B. J., Van der Heide-Wessel, C., and Van der Heide, R. M. (1984) Active and passive smoking in married couples: Results of 25 year follow up, *Br Med J* 288, 1801–1802.

Wald, N. J., Nanchanal, K., Thompson, S. G., and Cuckle, H. S. (1986) Does breathing other people's tobacco smoke cause lung cancer? *Br Med J* 293, 1217–1222.

Wells, A. J. (1986) Misclassification as a factor in passive smoking risk, *Lancet* II, 638.

Wu, A. H., Henderson, B. E., Pike, M. C., and Yu, M. C. (1985) Smoking and other risk factors for lung cancer in women, *J Nat Cancer Inst* 74, 747–751.

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Table A1. Annual U.S. male lung cancer deaths from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000	Nonsmoker Population 1000's	Fraction Exposed	Exposed Population 1000's	Relative Risk Constant at 2.1	
					Excess Death Rate	Deaths
35–39	1.8	5156	0.74	3815	1.09	42
40–44	2.9	4136	0.72	2980	1.78	53
45–49	4.5	3477	0.70	2440	2.80	68
50–54	7.0	3431	0.66	2260	4.46	101
55–59	11	3423	0.63	2155	7.15	154
60–64	16	3489	0.59	2054	10.7	219
65–69	23	3150	0.54	1695	15.9	269
70–74	33	2443	0.45	1099	24.3	267
75–79	49	1712	0.37	633	38.3	242
80–84	72	921	0.27	249	61.1	152
85+	95	516	0.08	41	96.0	39
Totals	15.9	31844	0.61	19420	8.26	1606

Appendix A

Details of death calculations

Tables A1 and A2 show the details of the death calculations for male lung cancer and female cancer other than lung and are similar in all respects to Table 6 in the text except that no declining relative risk calculation is shown for male lung cancer since the evidence that was available (Hirayama, 1984a) indicated no such decline.

In Table A3 the details are given for the development of the never smoker relative risks for heart disease that were used in the death calculations. As noted in the text, the 1963 neversmoker heart death rates by 5-year intervals were obtained by dividing the never smoker coronary heart deaths in Hammond's (1966) appendix, Table 14, by the person years in his appendix tables 2a and 2b. Reduction factors to account for the change in heart death rates between 1963 (end of Hammond's study) and 1984 were then developed by 10 year age intervals from the age specific heart death rates in table 24 of Health U.S. 1986 (NCHS, 1986). These reduction factors were modified for the fractions thought to be due to smoking which were taken from a staff report of the Office of Technology Assessment (OTA, 1985) to yield a combined never smoker reduction factor, interpolated back to 5-year age intervals, for application to the Hammond never smoker death rates. These modified rates, which are for enrollment age and therefore about 2 years younger than age of death, were then plotted against age of death on semi-log graph paper. Trend lines were then drawn through the female and the male points to yield the values in the last column of Table A3.

Tables A4 and A5 are simply the details of the heart death calculations as in Tables 6, A1, and A2 for cancer.

The deaths shown in Table 7 resulting from the corrections for misclassification were calculated from the relative risks in lines 4 of Table 5 taken as constant over the age range. The modification of the observed relative risks for smoker misclassification as shown in Table 5 are based on misclassified smoker relative risks calculated as follows. Based on as yet unpublished work of Wells on misclassification it was assumed that self-reported current smoker relative risks for male and female lung cancer in the U.S. and U.K. were 11 and 7, and 4.6 and 2.7 for male and female current smokers in Japan

Table A2. Annual U.S. female deaths from cancer other than lung from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000	Exposed Population (Table 6) 1000's	Relative Risk Constant at 1.16		Relative Risk Declining	
			Excess Death Rate	Deaths	RR	Deaths
35–39	28	5781	3.9	225	4.5	1321
40–44	48	4252	6.7	285	2.9	1411
45–49	80	3423	11.2	383	2.0	1449
50–54	125	3355	17.6	589	1.56	1579
55–59	190	3495	26.8	937	1.30	1591
60–64	265	3228	37.7	1219	1.18	1352
65–69	355	2912	51.1	1487	1.12	1144
70–74	470	2030	68.7	1395	1.08	729
75–79	600	1472	89.0	1310	1.05	431
80–84	750	547	114.7	627	1.034	138
85+	900	100	141.7	142	1.022	20
Totals	256	30595	28.1	8599		11165

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Table A3. Development of 1984 neversmoker heart death rates versus age.

Age Range	Death rates from Hammond (1966) at enrolled age per 100,000	Decline in heart DR's % 1963–84	Fraction of decline due to smoking	1984 Neversmoker Death Rate as % of 1963 (smoothed)	Hammond's N.S. D.R. corrected for decline	1984 Neversmoker heart death rate by age of death
Females:						
35–39	7.1	48	0	49	3.5	2.0
40–44	14.1			55	7.7	4.4
45–49	20.4	37	0	60	12.2	10.2
50–54	45.5			63	28.7	23
55–59	104	36	0	64	66	51
60–64	243			64	156	113
65–69	475	37	0	64	304	240
70–74	961			64	615	480
75–79	1648	35	0	65	1072	870
80–84	2774			70	1942	1550
85+	—	21	0	79	—	2770
Males:						
35–39	0	48	50	76	0	20
40–44	79.5			77	61	36
45–49	85.5	42	50	78	67	68
50–54	220			77	169	128
55–59	397	37.5	25	75	298	237
60–64	741			75	556	412
65–69	1089	32	25	76	827	730
70–74	1936			76	1472	1150
75–79	2639	25	10	77	2024	1850
80–84	4374			81	3543	2950
85+	—	14	10	86	—	4700

(Hirayama, 1984a). The 5% of ever smokers who were assumed misclassified as never smokers were assumed to consist of 23% light current smokers and 77% long term exsmokers. The excess risks for current, self-reported smokers were reduced by 2/3 to yield relative risks for misclassified current smokers and by 11/12 for relative risks of misclassified exsmokers essentially as was done by Wald *et al.* (1986). This resulted in misclassified ever smoker relative risks of 2.4, and 1.85 for males and females in the U.S. and U.K. and 1.5 and 1.25 for Japan. Worldwide misclassified smoker relative risks were then calculated to be 1.8 for males and 1.6 for females based on the proportion of "western" and "eastern" cases. The false relative risks shown on lines 2 in Table 5 were then calculated using the formulae in Wells' unpublished work.

For female cancer other than lung, the smoker relative risk of 1.05 was taken from Hammond (1966) and used as is since the effect is too small to make any difference. For ischemic heart disease the ever smoker relative risks from Hammond

Table A4. Annual U. S. female heart deaths from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000 (Table A3)	Exposed Population (Table 6) 1000's	Relative Risk Constant at 1.23		Relative Risk Declining	
			Excess D.R.	Deaths	RR	Deaths
35–39	2.0	5781	0.38	22	4.0	91
40–44	4.4	4252	0.84	36	2.0	97
45–49	10.0	3423	1.91	65	1.32	85
50–54	23	3355	4.4	148	1.17	114
55–59	51	3495	9.8	344	1.17	265
60–64	113	3228	22.1	713	1.17	548
65–69	240	2912	47.7	1385	1.17	1062
70–74	480	2030	97.2	1973	1.17	1505
75–79	870	1472	180	2647	1.17	2010
80–84	1550	547	334	1828	1.17	1374
85+	2700	100	607	607	1.17	451
Totals	291	30595	31.9	9768		7602

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Table A5. Annual U. S. male heart deaths from passive smoking

Age of Death	Neversmoker Death Rate per 100,000 (Table A3)	Exposed Population (Table A1) 1000's	Relative Risk Constant at 1.31		Relative Risk Declining	
			Excess D.R.	Deaths	RR	Deaths
35–39	20	3815	4.9	187	5.2	780
40–44	36	2980	8.9	265	3.0	879
45–49	68	2440	16.9	411	1.92	929
50–54	128	2660	32.1	724	1.42	951
55–59	237	2155	59.8	1289	1.28	1201
60–64	412	2054	105	2157	1.28	2009
65–69	730	1695	189	3195	1.28	2972
70–74	1150	1099	304	3341	1.28	3103
75–79	1850	633	500	3162	1.28	2933
80–84	2950	249	819	2039	1.28	1887
85–	4700	41	1377	565		520
Totals	521	19420	89.3	17335		18164

(1966) were taken as 2.3 for males and 2.0 for females. The excess risks were reduced by 2/3 to yield relative risks for misclassified ever smokers of approximately 1.4 for males and 1.3 for females. These were used worldwide with Wells' unpublished formulae to calculate the false heart disease relative risks shown on lines 2 of Table 5.

Appendix B

Relative risks for all causes of death and for emphysema and chronic obstructive lung disease

Data relating all causes of death with passive smoking for females have been reported for four prospective studies totalling 9537 cases as shown in Table B1. The combined relative risk is 1.165 with 95% confidence limits of 1.11 to 1.22. The only male data available are 75 cases from Gillis *et al.* (1984) with a relative risk of 1.0 so no male analysis was made.

The calculation of the total number of female deaths from all causes for passive smoking is shown in Table B2. The total, 34,164, is considerably larger than the total for cancer plus heart of 19,359 shown in Table 7. Some of the difference is due to uncertainties in the calculations, but other causes of death that might contribute to the all cause total, based on data in a private communication from Dr. Hirayama, are cerebrovascular disease, other heart disease, diabetes, and ulcer.

Hirayama (private communication, also reported preliminarily at 5th World Conference on Smoking and Health, Winnipeg, 1983) provides data relating deaths from emphysema with passive smoking in women. His relative risk, based on 106 cases is 1.3 with 95% confidence limits of 0.85 to 2.05. Kalandidi *et al.* (1987) report incidence data for chronic obstructive lung disease based on 103 cases with an adjusted relative risk of about 1.4. Lee *et al.* (1986) report incidence data for chronic bronchitis from spouse exposure. Based on 17 cases the adjusted relative risk is 1.22. A weighted average of these three relative risks would be about 1.35. The only neversmoker death rate we have is from Hammond (1966) for emphysema at 2×10^{-5}. Assuming 76% exposure, the excess death rate for passive smoking using Eq. (2) would be 0.55×10^{-5} and the total deaths for an exposed population of 30.6 million would be about 170. Even if this number is doubled to take into account deaths from forms of chronic obstructive lung disease other than emphysema, it is still far below the total for cancer and ischemic heart disease.

Table B1. Female relative risks for all causes of death from passive smoking.

	Locale	Total Cases	All Exposures		Mantel Trend
			RR	95% C.L.	1-tail p
Cohort Studies:					
Hirayama (1987)	Japan	9106	1.17[a]	1.12–1.23[a]	0.00001
Gillis *et al.* (1984)	Scotland	102	1.45	0.91–2.30	—
Garland *et al.* (1985)	California	79	1.06	0.65–1.73	—
Vandenbroucke *et al.* (1984)[b]	Holland	250	0.79	0.57–1.09	—
Combined Chort:		9537	1.165	1.11–1.22	

[a]Dr. Hirayama (private communication) provided the data necessary to calculate these items.
[b]*Data from 25 year follow up.* Relative risk was 0.89 (0.50–1.62) for 15 year follow up. This study is weak in that exsmoking women were included among the "nonsmokers," and nonsmoking women exposed to exsmoker husbands were included in the "nonexposed." The weakness of the study is emphasized in that the smoking women had a lower overall death rate (33.4%) than the nonexposed nonsmokers (38.1%).

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Table B2. Annual U.S. female deaths from all causes from passive smoking.

Age Range	Neversmoker Death Rates from Hammond (1966) at enrolled age per 100,000	Decrement due to heart death rate 1963–84 per 100,000	Corrected Neversmoker death rate at enrolled age per 100,000	Neversmoker death rate corrected to age of death per 100,000	Population exposed 1000's	Fraction of population exposed	Relative Risk Constant at 1.165 Excess D.R.	Deaths
35–39	136	3.6	132.4	120	5781	0.94	17.1	991
40–44	178	6.4	171.6	155	4252	0.92	22.2	944
45–49	254	8.2	245.8	212	3423	0.89	30.5	1044
50–54	352	16.8	335.2	300	3355	0.87	43.3	1452
55–59	561	38	523	445	3495	0.84	64.5	2254
60–64	867	87	780	675	3228	0.77	98.8	3190
65–69	1492	171	1321	1070	2912	0.70	158.3	4609
70–74	2585	345	2239	1830	2030	0.59	275.2	5586
75–79	4790	576	4214	3250	1472	0.49	496.1	7303
80–84	8408	832	7576	6000	547	0.29	944.8	5168
85+	—	—	—	10,000	100	0.10	1623	1623
Totals					30595		111.7	34164
Deaths per million total population								143

Lee *et al.* (1986) report data on chronic bronchitis life long nonsmoking in males exposed to a smoking spouse. Based on nine cases the adjusted relative risk was 0.34. However, for general exposure (4 cases) a positive relative risk was observed. No analysis of these data was attempted.

Appendix C

Rate difference model for assessing female ischemic heart deaths from passive smoking

A rate difference or absolute risk model was investigated for female ischemic heart disease in order to compare it to the relative risk models in ability to translate experience from one type of culture to another. Female ischemic heart disease was chosen because considerable data exist and because heart disease is the largest contributor to total deaths. Also, the relative risk model seems already to be well established for lung cancer (Wald *et al.*, 1986; Blot and Fraumeni, 1986) so a comparison in another disease category appeared to be appropriate.

Data from the four cohort studies (see Table 4) were combined using the direct pooling equations described on page 183 in Rothman (1986). The two case/control studies were omitted. Although their combined rate difference was essentially the same as that for the cohort studies, no good way could be found to combine it with that from the cohort studies. Death rates for exposed and not exposed populations were obtained by dividing the observed deaths in each category by person years which were equated to the mid-point populations multiplied by the years of followup. The rate difference was then obtained by subtracting the nonexposed death rate from the exposed death rate. Variances and weights were calculated by Rothman's formulae. The combined rate difference was obtained by summing the weighted rate differences and dividing by the sum of the weights. Confidence limits (95%) were equated to the rate difference $\pm 1.96\ (\text{variance})^{-\frac{1}{2}}$.

The results of these calculations are summarized in Table C1. The cohort data were also combined using Program 7 of Rothman and Boice (1982) with results essentially identical to those shown in Table C1 for direct pooling. The relative heterogeneity of the relative risks (*RR*) vs. the rate differences (*RD*) can be approximated by considering the range of *RR*-1 versus the range of *RD*. The range of *RR*-1 is from 0.16 to 2.6 for a factor of 16.3. The range of the rate differences is 3.7 to 262 or a factor of 71. The ratio for the two large studies, Helsing *et al.* (1988) and Hirayama (1984b), for *RR*-1 is 0.24/0.16 = 1.5 and for *RD* is 20.7/3.7 = 5.6. The 95% confidence limits for the rate ratio combination is tighter than for the rate difference combination. Also, the Hirayama study dominates the rate difference aggregation much more than in the rate ratio aggregation, providing 64% of the combined weight (last column of Table C1) in the rate difference case vs. only 17% of the combined weight in the rate ratio case.

Table C1. Rate difference calculations for female ischemic heart disease.

	Total Cases	Relative Risk from Table 4 RR	95% C.L.	Rate difference × 10^5 RD	95% C.L.	Weights for RD × 10^{-9}	RD × weight × 10^{-11}
Cohort Studies:							
Hirayama (1984b)	494	1.16	0.9– 1.4	3.7	−2.1– 9.6	1110	41.4
Gillis *et al.* (1984)	21	3.6	0.9–13.8	169.1	30.7–307.6	2	3.4
Garland *et al.* (1985)	19	3.5	0.9–13.6	262.2	36.0–488.4	0.8	2.0
Helsing *et al.* (1988)	988	1.24	1.1– 1.4	20.7	−0.2– 41.6	88	18.2
Combined Cohort	1522	1.23	1.1– 1.4	5.4	−0.2– 11.1	1201	65.0

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Table D1. Regional particle deposition from mouth breathing of side stream smoke.

Aerodynamic diameter μm	Cube of diameter	Relative concentration[a]	Relative Volume (Weight) per 0.1μm	Mass Distribution %	Fraction of inhaled particle mass deposited[b]			Mass deposited as % of total mass inhaled
					mouth throat	tracheo-bronchial	alveolar	
0.20	.008	1.5	0.006	0.3	0	0	0.13	0.04
0.25	.016	6.5	0.051	2.4	0	0	0.122	0.29
0.30	.027	10.0	0.135	6.4	0	0	0.115	0.74
0.35	.043	13.0	0.280	13.2	0	0	0.108	1.43
0.40	.064	13.0	0.416	19.6	0	0	0.10	1.96
0.45	.091	6.5	0.296	14.0	0	0	0.105	1.47
0.50	.125	3.5	0.328	15.5	0	0	0.11	1.71
0.60	.216	1.25	0.270	12.7	0	0	0.115	1.46
0.70	.343	0.5	0.172	8.1	0	0	0.12	0.97
0.80	.512	0.25	0.128	6.0	0	0	0.13	0.78
0.90	.729	0.05	0.036	1.7	0	0	0.14	0.24
1.00	1.0	0	0	0	0	0	0.15	0.00
			2.118	99.9				11.08

[a]From Hiller *et al.* (1982). Fig. 1.
[b]From Heyder (1984). Table 1. 250 cm³/second mean flow rate, 4 second breathing cycle.

This domination of the rate difference model by the Japanese study is evident from some rough death calculations. Use of the combined rate difference (5.4×10^{-5}) with the exposed female population from Table A4 (30.6 million) yields total deaths of 1,652 compared with 9,768 calculated from the constant rate ratio model. When the rate differences are plotted against age of death and weighted accordingly it is found that the "western" rate differences increase sharply with age whereas the Japanese rate difference stays constant at about 4×10^{-5}. Constructing a weighted average of these "western" and "eastern" death rates for each of the 5 year age ranges and multiplying by the corresponding exposed populations yields a total of about 2,100 deaths compared with 7,602 in the second relative risk model. Use of the Japanese data alone yields about 1,200 deaths. Use of only the "western" data (Gillis *et al.*, 1984; Garland *et al.*, 1988; Helsing *et al.*) at a constant rate difference yields 7,950 deaths while use of "western" data with the rate difference varying with age yields about 30,000 deaths. Thus, the death calculations using rate differences are quite volatile. Also, it is evident that with the rate differences it is not feasible to carry over the "eastern" experience, in ischemic heart disease at least, for use in a "western" setting. Accordingly, it was concluded that the absolute risk model is not as suited to combining risks for passive smoking as the relative risk models.

Table D2. Regional particle deposition from nose breathing of sidestream smoke.

Aerodynamic diameter μm	Mass distribution %[a]	Fraction of inhaled particle mass deposited[b]				Mass deposited as % of total mass inhaled	
		nose	mouth throat	tracheo-bronchial	alveolar	nose	alveolar
0.20	0.3	0	0	0	0.19	0.00	0.06
0.25	2.4	0.005	0	0	0.172	0.01	0.41
0.30	6.4	0.01	0	0	0.155	0.06	0.99
0.35	13.2	0.015	0	0	0.138	0.20	1.82
0.40	19.6	0.02	0	0	0.12	0.39	2.35
0.45	14.0	0.03	0	0	0.122	0.42	1.70
0.50	15.5	0.04	0	0	0.125	0.62	1.94
0.60	12.7	0.05	0	0	0.128	0.64	1.63
0.70	8.1	0.06	0	0	0.13	0.49	1.05
0.80	6.0	0.077	0	0	0.133	0.46	0.80
0.90	1.7	0.093	0	0	0.137	0.16	0.23
1.00	0.0	0.11	0	0	0.14	0.00	0.00
						3.45	12.99

[a]From Table D1.
[b]From Heyder (1984). Table 2. 250 cm³/second mean flow rate, 4 second breathing cycle.

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Table D3. Smoke Particle deposition patterns in direct and passive smoking.

	Direct Smoking	Passive Smoking	Direct/Passive
Entry site	Mouth	Nose	
Particulate inhaled per day, mg	240	2.8	86
Particle Size inhaled, μm	0.7	0.4	
Particle size exhaled, μm	0.7	0.4	
Retained in nose, %	0	3.5	
Retained in mouth, %	25	0	
Retained in tracheo-bronchial region, %	35	0	
Retained in near alveolar region, %	11	0	
Retained in deep alveolar region, %	9	13	
Total retained, %	80	16.5	
Particulate retained, total, mg	192	0.46	417
Particulate retained, alveolar, mg	48	0.36	133
Particulate retained, deep alveolar, mg	22	0.36	61

Appendix D

Dose considerations

As noted in the text, there is a wide difference between the observed disease ratio between passive and active smokers and the ratio of cigarette smoke particulate retained by each. Also, the cancer sites appear to differ. On the assumption that part of these differences may be due to differences in deposition sites between passive smoking and active smoking, calculations were carried out to try to pinpoint these differences.

The calculations for passive smoking are reasonably straightforward. Stöber (1984) has summarized all the uncertainties in this type of calculation. Nevertheless, the best approach appears to be to use the data of Hiller *et al.* (1982) for the particle size range of side stream smoke, centering around 0.4 μm, and the mathematical lung model of Heyder (1984) for inert particles. Integration of these two data sets yields a distribution of deposited weights by particle size for mouth breathing (see Table D1) which, when summed, yields exactly the total deposition observed by Hiller *et al.*, (1982) indicating that the Heyder model holds for passive smoking. The same inhaled particle size distribution can then be applied to Heyder's nose breathing case (see Table D2) which yields nasal deposition of 3.5% and deposition in the alveolar region of the lung of 13.0%. The model predicts zero deposition for both the mouth/throat and the tracheo-bronchial regions. From the deposition curves of Gerrity *et al.* (1979) (Fig. 2) for iron oxide extrapolated to a particle size of 0.25 μm (which is equivalent to an aerodynamic diameter of 0.4 μm) it appears that all of the lung deposition from passive smoking probably occurs deep in the alveolar region at generation 19 or beyond. Black and Pritchard (1984) have determined the half-time for alveolar retention for direct cigarette smoke to be 17 hours indicating that the smoke particles dissolve and clear into the blood or lymph system. There is every reason to believe that the passive smoke particles clear the same way.

With direct smoking there has so far been no model developed that explains the observed phenomena, namely that the inhaled particle size is about 0.7 μm, that 70% to 80% of the inhaled smoke is retained, that 15 to 35% is retained in the mouth, and that the exhaled particle size is also about 0.7 μm. The Heyder model at 0.7 μm would predict total retention of only 12%. To achieve 75% retention, the Heyder model would require an effective particle size of 6.5 μm. Main stream smoke is known to agglomerate, but if it agglomerated to 6.5 μm, the exhaled smoke, according to the Heyder model, would be about 6 μm, much too large compared to that observed. Mitchell (1962) observed that direct smoke particles grow in the mouth to about 1.15 μm and that the smoke exhaled from the lung after a 5 second retention period had a mass median diameter size of 0.65 μm. Let us assume that the 0.65 μm part of the smoke follows Heyder's model and that 20% of the total smoke inhaled was exhaled, all from the 0.65 μm fraction. The inhaled part of the smoke corresponding with the 0.65 μm part exhaled would have the same particle size and would deposit about 12%, deep in the alveolar region. This is 12% of 22.7% of the total smoke inhaled, or 2.7% of the total inhaled smoke. The balance of the inhaled smoke (77%) would have a larger average particle size, about 1.3 μm. Black and Pritchard (1984) found, based on clearance data, that the rates of alveolar deposition to alveolar plus tracheo-bronchial deposition in direct smoking is 0.36. Also, as noted, some amount, say 25% of the total inlet smoke should deposit in the mouth and throat, all of which would have to come from this larger size fraction. Summarizing these numbers, of the 100 − 20 − 25 = 55% of total smoke particulate that reaches the lung and is not exhaled, 0.64 × 55 = 35% deposits in the tracheo-bronchial region and 0.36 × 55 = 20% deposits in the alveolar region. We have already accounted for 3% of the alveolar deposition from the 0.65 μm particles. The remaining 17% would come from the larger particles. Based on the alveolar/tracheo-bronchial split and using the curves of Gerrity *et al.* (1979) it would be expected that about 2/3 of the alveolar deposit or 11% would deposit in the "near" alveolar region, generations 16–18, and 6% in the "deep" alveolar region, generations 19–21, for a total "deep" alveolar deposition of 9%. These calculations are summarized in Table D3.

Just what the mechanisms are for so much direct smoke deposition remains unclear. Certainly impaction and sedimentation (the Heyder model) do not account for it. Stöber (1984) suggests that electrical charges in the newly generated smoke particles (see Melandri *et al.*, 1983) may account for some of it. Another possible mechanism is the cloud settling phenomenon as described by Fuchs (1964).

Whatever the mechanism, a reasonably clear idea of the regional deposition patterns from direct and passive smoking

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can be obtained as shown in Table D3. The nasal deposition from passive smoking could account for the observed nasal sinus cancer. Also, if the observation of Balin *et al.* (1986) is correct that there is a direct passage for toxics from the nose to the brain, it could also account for the observed brain cancer. In the deep alveolar region the ratio of direct to passive deposition is much closer to the inhaled ratio than to the "total retained" ratio. It is from the deep alveolar region that the smoke particles are solubilized and cleared into the blood and lymph systems possibly to cause cancers of the liver, breast and endocrine glands, leukemia, lymphoma and arterial plaques.

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Meta-Analyses on Passive Smoking and Lung Cancer

H. Letzel and K. Überla

Summary

Up to now, meta-analysis has rarely been used in epidemiology and no generally accepted standards are available. Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers.

In our paper two cohort and ten case-control studies were analyzed using several statistical techniques (Fisher, Mantel-Haenszel, Yusuf). Only data from women were included and a quality indicator (histology exposure, methodology) was used to analyze different study combinations, i.e. an analysis of sensitivity was performed. For the Hirayama study two different risk estimates were used. In addition, all 1,023 logically possible combinations of the 10 case-control studies were analyzed.

Of all possible meta-analyses of the 10 case-control studies, 670 (65.5%) were not significant at $P \leqq 0.05$ (Yusuf technique). The Trichopoulos study is involved in 330 of the 353 significant study combinations, indicating that this is the dominating case-control study, although the methodological quality is unacceptable.

Combining case-control and cohort studies, the relative risk estimates range from 1.013 to 1.118, depending on the specific subset of studies analyzed. These relative risk estimates include unity. The quality of the individual studies is highly variable and sometimes poor. We conclude that as long as no better studies are available, meta-analyses cannot and do not add much new evidence to the question of whether passive smoking is related to lung cancer.

Up to now, meta-analyses have mainly been used with randomized clinical trials. The technique has been criticized [6, 10, 23] for various reasons. Standards for meta-analyses in epidemiology are not yet available. Bias by non-reporting of studies, by selecting certain subgroups or by redefining sample sizes can create additional difficulties for a statistical evaluation. How different study designs – e.g. case-control versus cohort studies – should be weighted is left to the investigator. It is not surprising that the application of such methods in a controversial field like passive smoking and lung cancer does not come up with uniform results.

The inclusion of studies in meta-analyses is justified as long as there are no major methodological shortcomings in the individual studies. Combining biased or confounded results by meta-analysis cannot provide correct answers. There is a strong case for an analysis of sensitivity [23]. It investigates the effect of different study selections as well as the impact of different statistical methods on the results.

When the first papers on passive smoking and lung cancer were published a serious hypothesis was created [11, 27]. This hypothesis is serious because – if it is right – thousands of non-smokers are being killed worldwide by smokers. But the hypothesis is also serious because – if it is wrong – smokers are being accused of killing other people without actually doing so.

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Last year Wald [31] published the first meta-analysis of the available studies on passive smoking and lung cancer. In his paper the results obtained in men were included, and in two studies the subgroup of women married to ex-smokers was excluded. The quality of the individual studies was not taken into account and no analysis of sensitivity was performed.

Every meta-analysis has to state its goals, criteria and methods before it starts. In our analysis we planned

1) to include only studies which fulfil minimal methodological requirements. We wanted to eliminate statistical noise.
2) to select carefully the "best" relative risk estimate from every study, not just the one which was reported by the authors or the highest one.
3) to classify the quality of the studies regarding determination of histology, estimation of exposure and overall study methodology.
4) to use different statistical techniques, namely the Fisher method and the method used by Yusuf [32] or Wald [31].
5) to study the sensitivity of the results with regard to including different subsets of studies depending on their qualities.

Selection of Studies

We did not include the studies by Gillis [9], Knoth [16], Miller [22] and Sandler [24–26]. These studies do not fulfil minimal methodological criteria and they do not contain relevant information. Only insufficient data are available from them. Wald [31] had included the Gillis study [9], which only has 14 non-smoking lung cancer cases and correspondingly wide confidence intervals contributing nothing to the available evidence.

We also excluded men because the majority of evidence comes from studies in women. Only about 11% of the reported cases are men. Their results vary widely. There is not a single significant result in men. The situation regarding biology, exposure and reporting habits is considerably different in men as compared to women.

We included two cohort studies [7, 12–14] and 10 case-control studies [1–5, 8, 15, 17, 19–21, 27, 28]. These studies had also been included by Wald [31]. The only difference is that we didn't include the Gillis study [9] and that we restricted our analysis to women. The availability of histology, the quality of the exposure indicator and an overall quality rating of the study were judged by K. Überla. Three study groups resulted: cohort studies, case-control studies with reasonable quality (quality +) and case-control studies with poor quality (quality −) (Table 1).

The 2×2 tables and RR estimates for the 12 studies used are presented in Table 2. Generally, these numbers are the same as used by Wald [31] with the exception that we did not exclude the wives of ex-smokers in the studies by Hirayama [14], Trichopoulos [27, 28] and Koo [17].

Regarding the Hirayama study we did not use a relative risk estimate of 1.63 as did Wald [31]. In a subsequent paper by Überla and Ahlborn [30], which will be presented in this session of the conference, it is shown that, when one adjusts the Hirayama cohort to the age of the female population in Japan, the relative risk is 0.90. We alternatively used a risk estimate of 1.45 for the Hirayama study. This was calculated from Table 2 of the 1984 publication by Hirayama [13] and was standardized by the age of women only.

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Table 1. Quality rating of studies selected for meta-analyses

Author	Histology	Exposure	Quality rating**	Resulting group
Hirayama	−*	−	3	Cohort
Garfinkel	−	−	2	Cohort
Chan et al.	±	+	4	CC quality +
Correa et al.	−	±	5	CC quality −
Trichopoulos et al.	−	±	6	CC quality −
Buffler et al.	+	−	4	CC quality +
Kabat et al.	+	+	4	CC quality +
Garfinkel et al.	+	+	4	CC quality +
Akiba et al.	−	−	5	CC quality −
Lee et al.	−	+	5	CC quality ±
Koo et al.	±	+	4	CC quality +
Pershagen et al.	+	+	4	CC quality +

The included studies are the same as in the paper by Wald et al. (1986). We included women only.
** 2 = acceptable; 3 = possibly flawed; 4 = bias and confounding suspected; 5 = major bias and confounding suspected; 6 = unacceptable

Table 2. 2 × 2 Tables and relative risk estimates for studies selected for meta-analyses

Author	Exposed lung cancer		Unexposed lung cancer		Relative risk
	+	−	+	−	
Hirayama	163	69,428	37	21,858	1.45 (1) 0.90 (2)
Garfinkel	88	127,164	65	49,422	1.18
Chan et al.	34	66	50	73	0.75
Correa et al.	14	61	8	72	2.03
Trichopoulos et al.	53	116	24	109	2.01
Buffler et al.	33	164	8	32	0.80
Kabath et al.	13	15	11	10	0.79
Garfinkel et al.	91	254	43	148	1.23
Akiba et al.	73	188	21	82	1.48
Lee et al.	22	45	10	21	1.03
Koo et al.	66	97	22	40	
Pershagen et al.	33	150	34	197	1.27

The underlined numbers are different from those assumed by Wald. We did not exclude the wives of ex-smokers.

(1) Hirayama standardized by age of women only (from Table 2, Hirayama 1984)
(2) Hirayama with age selection bias removed (Überla and Ahlborn, 1987)

Results

Meta-Analyses for All Possible Case-Control Study Combinations

In order to get a feeling for the consequences of random selection of studies, we first considered all possible combinations of case-control studies. With 10 case-control studies there are 1,023 possible study combinations or subsets for which a meta-analysis can be performed. We calculated them all. The results can be summarized as follows:

34.5% of all possible meta-analyses – using the Yusuf technique – are technically significant at $p \leqq 0.05$. That means that a random selection of studies leads to a probability of 65.5% for a negative result of the meta-analysis.

The Trichopoulos study is involved in 330 of the 353 significant study combinations, that is in 93.5%. This study is the dominant study in the significant combinations. Without the Trichopoulos study only 23 out of the 511 then possible study combinations are "significant", that is 4.5%. One has a probability of 95.5% for a negative result selecting a subset of studies for a meta-analysis randomly.

The Trichopoulos study was judged as methodologically unacceptable. It is a textbook example of how a case-control study should not be performed [29]. If it were included, however, the impact of this study on the results would prove to be heavy.

Table 3. Results of meta-analyses I

Author		Cohort only	Case-control quality +	Case-control quality −	Cohort plus CC quality +	All
Hirayama*		×			×	×
Garfinkel		×			×	×
Chan			×		×	×
Correa				×		×
Trichopoulos				×		×
Buffler			×		×	×
Kabath			×		×	×
Garfinkel			×		×	×
Akiba				×		×
Lee				×		×
Koo			×		×	×
Pershagen			×		×	×
Fisher:	p	0.017	0.604	0.007	0.137	0.009
Yusuf:	$\widehat{RR}$	1.271	1.074	1.652	1.178	1.260
	IL 95	1.025	0.848	1.201	1.005	1.093
	IU 95	1.575	1.361	2.272	1.381	1.453
	p**	0.014	0.277	0.001	0.022	0.001

* Hirayama standardized by age of women only, RR = 1.45 as calculated from Table 2, Hirayama, 1984
** one-tailed

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Table 4. Results of meta-analyses II

Author		Cohort only	Cohort plus CC quality +	All without Trichopoulos	All
Hirayama adjusted*		×	×	×	×
Garfinkel		×	×	×	×
Chan			×	×	×
Correa			–	×	×
Trichopoulos			–	–	×
Buffler			×	×	×
Kabath			×	×	×
Garfinkel			×	×	×
Akiba			–	×	×
Lee			–	×	×
Koo			×	×	×
Pershagen			×	×	×
Fisher:	p	0.105	0.336	0.158	0.028
Yusuf:	$\widehat{RR}$	1.013	1.035	1.076	1.118
	IL 95	0.848	0.941	0.941	1.273
	IU 95	1.210	1.193	1.230	1.299
	p**	0.443	0.317	0.142	0.046

* With age selection bias removed. RR = 0.902 (Überla and Ahlborn 1987)
** one-tailed

Meta-Analyses for Selected Study Groups

Meta-analyses for various combinations of cohort and case-control studies were calculated. The results are given in Table 3. For the Hirayama study a relative risk of 1.45 for the exposed versus non-exposed persons is used in all these combinations as one of the starting points. The results show that the probability using the Fisher method is always higher than the probability using the procedure as applied by Yusuf [32] or Wald [31]. This had to be expected. The other methods – Mantel-Haenzsel or for the cohort studies risk ratios – do not differ much from the Yusuf method. All the study combinations on Table 3 are significant with the exception of the reasonable quality case-control studies. These six studies have a common risk estimate of 1.07, being not statistically different from unity.

The meta-analyses for these study combinations were repeated using a relative risk of 0.90 for the Hirayama study as was calculated by Überla and Ahlborn [30]. The pooled risk estimates are very close to unity and are not statistically significant (Table 4). When one includes the Trichopoulos study, the pooled estimate for the relative risk is 1.118, approaching but not reaching statistical significance.

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Discussion

To summarize, the expected overall risk of dying of lung cancer for non-smoking women married to smoking men is:

- 1.074 out of six case-control studies of reasonable quality,
- 1.013 out of two prospective studies, using the Hirayama study with the age selection bias removed as shown by Überla and Ahlborn,
- 1.035 out of two prospective studies and six case-control studies of reasonable quality,
- 1.076 out of eleven studies, with the Trichopoulos study excluded, and
- 1.118 out of all twelve studies including the Trichopoulos study.

These risk estimates are not statistically different from unity.

Thus, the overall result of various meta-analyses can be summarized as follows: Meta-analysis of 12 relevant studies (using women only and adjusting the relative risk of Hirayama for age selection bias) gives an overall estimate of relative risk of dying of lung cancer for non-smoking women married to smoking men of $\widehat{RR} = 1.076$ (Trichopoulos excluded) or $\widehat{RR} = 1.118$ (Trichopoulos included). These risk increases of about 8% or 12% are not significantly different from unity.

Our results differ widely from the results given by Wald [31]. The main reasons are different relative risk estimates for the individual studies. The papers by Hirayama and Trichopoulos were the first studies to be published on this issue. All later studies give less indicative results. Whether wives of ex-smokers should be included or not, whether the Hirayama study has to be adjusted for age selection bias and whether the Trichopoulos study is methodologically as stringent as a case-control study should be is open for discussion and will be answered differently by individual scientists. We have shown a variety of possible outcomes of meta-analyses and demonstrated the sensitivity of the results with varying assumptions.

The whole question of meta-analyses comes down to the question of the quality of the individual study. As long as there are no better studies available, meta-analyses cannot and do not add much new evidence to the question whether passive smoking is related to lung cancer.

References

1. Akiba S, Kato H, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Res 46:4894–4807
2. Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. In: Grundmann E (ed) Cancer campaigne, vol 6. Cancer epidemiology. Gustav Fischer, Stuttgart, pp 199–202
3. Correa P, Pickle LW, Trontham E, Lin Y, Haenszel W (1983) Passive smoking and lung cancer. Lancet 2:595–597
4. Correa P, Pichler LW, Trontham E, Dalager E, Haenszel W (1984) The causes of lung cancer in Louisiana. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Chemie, Weinheim, pp 73–82
5. Dalager NA, Pickle LW, Mason ThI, et al (1986) The relation of passive smoking to lung cancer. Cancer Res 46:4808–4811
6. DerSimonian R, Laird N (1986) Meta-Analysis in Clinical Trials. Controlled Clinical Trials 7:177–188
7. Garfinkel L (1984) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J Natl Canc Inst 66:1061–1066

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8. Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: a case control study. J Natl Canc Inst 75:463–469
9. Gillis CR, Hole DJ, Hawthorne VM, Boyle P (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Respir Dis (Suppl) 133:121–126
10. Grahame R (1978) Comparison of different trials. Rheumatol Rehabil (Suppl) 135–139
11. Hirayama T (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 282:183–185
12. Hirayama T (1983) Passive smoking and lung cancer. Consistency of association. Lancet 1:1425–1426
13. Hirayama T (1984) Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P (eds) Lung cancer: causes and prevention. Chemie, Weinheim, pp 175–195
14. Hirayama T (1984) Cancer mortality in non-smoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 13:680–890
15. Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221
16. Knoth A, Bohn H, Schmidt F (1983) Passivrauchen als Lungenkrebsursache bei Nichtraucherinnen. Med Klin 78:66–69
17. Koo LC, Ho JHC, Saw D, Path C (1983) Active and passive smoking among female lung cancer patients and control in Hong Kong. J Exp Clin Cancer Res 4:367–375
18. Koo LC, Ho JHC, Saw D, Path C (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J Exp Clin Cancer Res 3:277–283
19. Koo LC, Ho JHC, Lee N (1985) An analysis of some risk factors for lung cancer in Hong Kong. Int J Cancer 35:149–155
20. Lee PN (1984) Lung cancer incidence and type of cigarette smoked. In: Mizell M, Correa P (eds) Lung cancer: Causes and prevention. Chemie International, Deerfield Beach, pp 373–384
21. Lee PN, Chamberlain J, Alderson HR (1986) Relationship of passive smoking to risk of lung cancer and other smoking diseases. Br J Cancer 54:97–105
22. Miller GH (1984) Cancer, passive smoking and nonemployed and employed wives. West J Med 140:632–635
23. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers ThC (1987) Meta-analyses of randomized controlled trials. N Engl J Med 316:450–455
24. Sandler DP, Everson RB, Wilcox AJ (1984) Passive smoking in adulthood and cancer risk. Am J Epid 121:37–48
25. Sandler DP, Wilcox AJ, Everson RB (1985) Cumulative effects of lifetime passive smoking on cancer risks. Lancet 1:312–315
26. Sandler DP, Everson RB, Wilcox AJ, Browder JP (1985) Cancer risk in adulthood from early life exposure to parents smoking. Am J Publ Health 75:487–492
27. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1–4
28. Trichopoulos D, Kalandidi A, Sparros L (1983) Lung cancer and passive smoking: conclusion of Greek study. Lancet 2:677–678
29. Überla K (1987) Lung cancer from passive smoking: hypothesis or convincing evidence? Int Arch Occup Environ Health 59:421–437
30. Überla K, Ahlborn U (1987) Passive smoking and lung cancer: a reanalysis of Hirayama's data. International Conference on Indoor Air Quality. Tokyo
31. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS (1986) Does breathing other people's tobacco smoke cause lung cancer? Br Med J 293:1217–1222
32. Yusuf S, Peto R, Lewis J, Collins R, Sleight P (1985) Beta blockade during and after myocardial infarction: an overview of the randomized trials. Progress in Cardiovascular Diseases Vol XXVII 5:338

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Epidemiological Issues on Involuntary Smoking and Lung Cancer

Y. Shimizu, T. Namekata, and K. Takemoto

Summary

Both case-control and cohort studies of passive smoking and lung cancer published since 1981 were reviewed with the intent to make recommendations for future epidemiologic study of this controversial topic. The relative risk of lung cancer among non-smoking women married to smoking men compared to non-smoking women married to non-smoking men varied considerably over a range from 0.75 to 3.4 dependent on sample size, histological type studied, type of questionnaire administered, case ascertainment method, country or nationality of the study population, and age of the study population [28]. Major possible sources of bias and misclassification have been considered by other investigators and committees [22, 28]. Some new observations are made on these already carefully scrutinized data and an attempt is made to give concrete solutions for solving the problems of low-level risk assessment of this indoor environmental air pollutant and its potential carcinogenic effect.

Introduction

Since the disclosure of the 1964 Surgeon General's report [29], cigarette smoking has been labeled one of the most insidious health hazards encountered by humans in the twentieth century. With the establishment of tobacco smoke as a carcinogen, the question arises: If tobacco smoke is hazardous to those who directly inhale it, then what are the possible health consequences to an individual who breathes this potential carcinogen on a second hand basis by sharing the same air space as an active smoker?

This issue has ignited a conflagration of public debate, beginning in 1981 [11], due to the involuntary nature of exposure to environmental tobacco smoke (ETS) in the workplace and at home. Scientific debate is ongoing, involving careful scrutiny of the dozen or so reports of the effects of ETS on lung cancer incidence.

An epidemiological review of the relevant papers was conducted to improve future studies of passive smoking and lung cancer and the following general observations were made:

1) The age range of subjects in some studies was inappropriate to allow for latency of the outcome of interest (lung cancer) to occur;
2) Adequate statistical power was not obtained in many studies due to small numbers of cases and controls;
3) Misclassification of the disease variable (lung cancer), of case or control eligibility (non-smokers), and of the exposure variable (smoking spouse) is not only possible but probable to some degree in all of the studies reviewed;

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META-ANALYSIS IN EPIDEMIOLOGY, WITH SPECIAL REFERENCE TO STUDIES OF THE ASSOCIATION BETWEEN EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER: A CRITIQUE

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Abstract—Meta-analysis, a set of statistical tools for combining and integrating the results of independent studies of a given scientific issue, can be useful when the stringent conditions under which such integration is valid are met. In this report we point out the difficulties in obtaining sound meta-analyses of either controlled clinical trials or epidemiological studies. We demonstrate that hastily or improperly designed meta-analyses can lead to results that may not be scientifically valid. We note that much care is typically taken when meta-analysis is applied to the results of clinilcal trials. The Food and Drug Administration, for example, requires strict adherence to the principles we discuss in this paper before it allows a drug's sponsor to use a meta-analysis of separate clinical studies in support of a New Drug Application.

Such care does not always carry over to epidemiological studies, as demonstrated by the 1986 report of the National Research Council concerning the purported association between exposure to environmental tobacco smoke and the risk of lung cancer. On the basis of a meta-analysis of 13 studies, 10 of which were retrospective and the remaining 3 prospective in nature, the Council concluded that non-smokers who are exposed to environmental tobacco smoke are at greater risk of acquiring lung cancer than non-smokers not so exposed. In our opinion, this conclusion in unwarranted given the poor quality of the studies on which it is based.

I. INTRODUCTION

A working definition of meta-analysis is given by Huque [1]: "...the term 'meta-analysis' refers to a statistical analysis which combines or integrates the results of several independent clinical trials, considered by the analyst to be 'combinable'." As indicated by this characterization of meta-analysis, its key application is to be found in the analysis and synthesis of data from clinical trials.

The question then remains, can meta-analytic techniques be applied in the analysis of other kinds of data such as those that arise in cohort and case–control studies found in epidemiology? The answer to this question is a guarded "yes." The criteria for reaching this affirmative answer are now considered.

In applications of meta-analysis to clinical trials, the following questions, among many other that must be addressed, arise.

- Are all studies to be included in the meta-analysis, or only the published ones?
- Are all published studies to be included in the meta-analysis, or only the "good" ones?
- When the studies' results are heterogeneous, how may they be included in a meta-analysis, or should they be meta-analyzed at all?
- Within each study, should all subjects in a treatment group be considered in a

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meta-analysis, or only those subjects who were compliant with the treatment? The same question applies to subjects in the control group.

Similar issues are of concern in epidemiological studies. However, when case–control studies are under consideration, the issue of "intention-to-treat," which is the final question just listed with regard to meta-analysis in clinical trials, is not of direct concern. Instead, the following additional question needs to be addressed in a meta-analysis of case–control epidemiological studies.

- Has proper control or adjustment been made for the biases that frequently occur in epidemiological studies, such as sociodemographic or clinical differences between study populations, misclassification of subjects with regard to case–control status and to levels of exposure, factors other than the level of exposure that may affect whether a subject is a case or control (i.e. confounding variables), and the publication bias/file drawer phenomenon wherein studies that fail to show a positive association tend not to be published and are thus not candidates for inclusion in the meta-analysis?

Meta-analysis was first applied to the study of psychotherapy and to the study of educational interventions (see Hedges and Olkin [2], for example), and is now widely used to provide overviews of randomized controlled clinical trials. It is also applied in the synthesis of data from epidemiological case–control studies, but, as will be covered in Section III, with uncertain theoretical justification.

Among the principal uses of a properly performed meta-analysis are:

- To increase statistical power for important endpoints and subgroups.
- To resolve controversy when studies disagree.
- To improve estimates of effect size.
- To answer new questions that were not previously posed in the individual studies.

How meta-analysis is applied in both randomized clinical trials and epidemiological case–control studies are the topics of Sections II and III of this paper. Special emphasis will be placed on epidemiological studies of the hypothesized association between exposure to environmental tobacco smoke and lung cancer.

II. APPLICATIONS OF META-ANALYSIS TO CLINICAL TRIALS

Before reviewing and criticizing the application of meta-analysis to epidemiological studies, it is worthwhile to review and critique its application to a methodologically stronger kind of study, the randomized controlled clinical trial. We shall identify a number of areas of uncertainty and controversy concerning such applications, present the points on which consensus seems to exist, and then use the results of this review as a template for our critique of meta-analyses of studies in epidemiology.

Analyze all published studies or only the "good" ones?

In their review of published meta-analyses, Sacks *et al.* [3] found that nearly 30% of them combined results from both randomized and non-randomized studies. If there is unanimity among meta-analytic methodologists on any issue, however, it is on the requirement that only randomized clinical trials be included in a meta-analysis [4–8]. These experts take it as axiomatic that the potential for bias in the non-randomized assignment of patients to treatment groups is too great for the results of such studies to be trusted. There exist examples of non-randomized studies that are, in other respects, superior in quality to randomized studies [9], but the concern about the quality of non-randomized studies in general is a valid one. The principle that meta-analyses be restricted to randomized studies is by-and-large appropriate.

Having agreed on the criterion of non-randomized treatment assignment for excluding a study from a meta-analysis, the experts disagree on other possible criteria for excluding studies (absence of double-blinding, efficacy rather than intention-to-treat analysis, study is out of date, etc.), and indeed disagree on whether any randomized trial, no matter how poorly designed, should ever be excluded [7,8,10]. Hedges, for example, suggests that it is standard procedure in meta-analyses in the physical sciences to delete experiments that are deemed to be flawed [11]. H. J. Eysenck, a British psychologist and philosopher of science, labels as "mega-silliness" the practice of including methodologically inadequate research in a meta-analysis [12].

Chalmers and his colleagues have developed rigorous, reproducible and unbiased methods for measuring the quality of a study [13]. One

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may use the derived measurements to decide whether to accept or reject the study for a meta-analysis, to determine in a formal [14] or informal [15] way whether a study's quality and its estimate of treatment effect are correlated, or to weight studies differentially according to their measured qualities (such a suggestion was recently made by Jenicek [16]). One way to carry out this latter strategy is to modify the meaning of the weight to be assigned to a study's estimated treatment effect, e, in the weighted average

$$\bar{e} = \Sigma we / \Sigma w.$$

In most applications of meta-analysis, w is roughly proportional to the total number of patients in the study. If q is the study's value on the measure of quality, perhaps scaled to vary from 0 to 1, the proposed overall measure of the effect of treatment is

$$\bar{e} = \Sigma (qw)e / \Sigma (qw).$$

A large study whose quality is good will receive all or nearly all of the weight it is entitled to, whereas a study of comparable size but measurably poorer quality will have its contribution to the weighted average correspondingly reduced.

We are not aware of any meta-analyses in which the measures of quality have actually been formally incorporated into the analysis. The proposed method is novel, and worth a critical evaluation.

Analyze all studies or only the published ones?

When planning a meta-analysis, the investigator must decide whether to analyze only those studies that had been published or to analyze as well studies that had not been published. Apparently, no consensus has yet been reached concerning which strategy to adopt. Yusuf [8] recommends that the results of both published and unpublished controlled trials be considered for analysis; he and his colleagues were successful in locating several unpublished studies in an influential meta-analysis of the effects of beta blockers after myocardial infarction [17]. Abstracts of papers presented at meetings and abstracts of master's theses and doctoral dissertations were perused in the pioneering meta-analyses of studies evaluating the efficacy of psychotherapy [18]. Chalmers *et al.* [4] have warned, however, that even a systematic and rigorous attempt at obtaining the results of all unpublished studies may produce bias or unduly decrease precision.

There are two main reasons for including unpublished studies in a meta-analysis. One is to overcome "publication bias," the acknowledged tendency of reviewers to recommend against and of editors to decide against publishing studies that failed to show an effect of treatment. The other is to overcome the bias due to the related "file drawer phenomenon," the tendency on the part of the author not even to bother submitting for publication an article that fails to show an effect [19]. If either of these two sources of bias operates, then a meta-analysis only of results reported in published articles will tend to overstate the degree of statistical significance of the treatment's effect, and to overestimate that effect. An alternative to the difficult task of searching for unpublished studies is to attempt to undo this bias by applying statistical adjustments to the data [20,21]. These statistical procedures are still too new for them to have been theoretically and empirically evaluated. Thus, effectively, the publication bias/file drawer issue remains a serious problem in performing a meta-analysis. The careful and thorough search for unpublished studies is an expensive and time consuming endeavor, and may uncover studies of uncertain quality, but no validated alternative is currently available.

Analyze only homogeneous studies?

Some statistical reviewers at the U.S. Food and Drug Administration have strongly criticized the pooling of results from controlled clinical trials in which there is *heterogeneity of treatment effect*— i.e. sizable differences exist between studies in their estimates of the effect of treatment—and have suggested that it is valid to combine results only from studies in which the estimates are sufficiently close one to another [22,23]. Stein, in fact, denigrated as a mere "computational exercise" the meta-analysis of studies in which the estimated treatment effects were heterogeneous [23]. Sacks *et al.* refer to this criterion as *combinability* [3].

Fairly straightforward statistical methods exist to test the hypothesis of heterogeneity for both continuous measurements [24] and categorical data [25] (see the statistical Appendix), although not all FDA reviewers are in agreement as to how strict the statistical criteria should be for deciding that different studies are combinable [1]. Furthermore, it is not clear that these reviewers would accept as evidence for efficacy the finding of a statistically significant

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pooled effect even if the meta-analysis was restricted to studies that were combinable.

Some justification may be granted to the tough stand taken by these FDA reviewers, as they are responsible for interpreting and applying regulations handed down to them. In settings other than regulatory ones, however, it is not obvious that the criterion of combinability must always be satisfied before a meta-analysis may be applied. DeMets, for example, questions the meaning that attaches to the overall results of a meta-analysis when there is heterogeneity across studies [26]. Others, however, suggest that it is precisely when studies differ with respect to the magnitude and perhaps even the direction of treatment effect that the formal methods of meta-analysis are needed to summarize in an unbiased manner all of the information available to date [6,27]. With respect to the possibility that the effect of a treatment is strongly positive in one study and strongly negative in another, Peto states that "(this) situation... would be unusual, although certainly not impossible" [6, p. 233]. The frequency with which such a *qualitative interaction* occurs may be greater than he and others (including the two authors of this paper) have believed. A recent randomized controlled trial of the post-infarction effect of a calcium channel blocker, for example, found this very kind of interaction [28].

Whether and how to carry out a meta-analysis in the presence of heterogeneous effects are still unanswered questions. There appears to be only one point on which there is agreement: it is invalid to delete from the set of studies to be meta-analyzed those whose results are in the "wrong direction," for the opportunity for bias in identifying the "deviant" studies is too great. Furthermore, one would be left drawing the inane conclusion that "in those studies in which the treatment effects were in the same direction (all positive, all negative, or all close to zero), the overall effect of treatment was also in that direction."

Intention-to-treat vs efficacy analysis

The controversy that exists concerning the appropriate samples of patients to be analyzed within a single trial carries over into the realm of meta-analysis. According to the intention-to-treat principle, patients are to be analyzed within the treatment groups they were randomly assigned to, no matter how much or how little treatment they actually received [29].

In an efficacy analysis, on the other hand, only data from compliant patients are analyzed [30]. Sack *et al.* found, in their review, that 9 of 19 meta-analyses that considered this issue restricted their analyses to studies that employed the intention-to-treat principle, and 9 analyzed data from either kind of study [3]. Only one meta-analysis restricted attention to studies in which efficacy analyses were performed. Because efficacy analyses tend to produce overestimates of a treatment's effect, and intention-to-treat analyses tend to produce underestimates, caution suggests that, when sufficient information is provided to ascertain which approach was used, only studies that analyzed data from the more conservative intention-to-treat perspective be included in a meta-analysis. When studies that performed only efficacy analyses are included in a meta-analysis, one may expect that some degree of bias toward greater significance and toward an overestimation of the effect of treatment is present.

Data presentation

Most theorists and many practitioners of meta-analysis agree that a graphic display of the individual studies' results and of the overall, pooled result is invaluable. Most often, each study's estimated treatment effect (expressed as a relative risk when the outcome is morbidity or mortality) is marked by a circle or tick mark, and 95 or 99% confidence limits about the estimate are displayed as straight lines extending to the left and to the right of the point estimate (see Fig. 1). The several studies' lines appear one above the other, and the last line indicates the value of the summary estimate pooled across all individual studies, along with its confidence

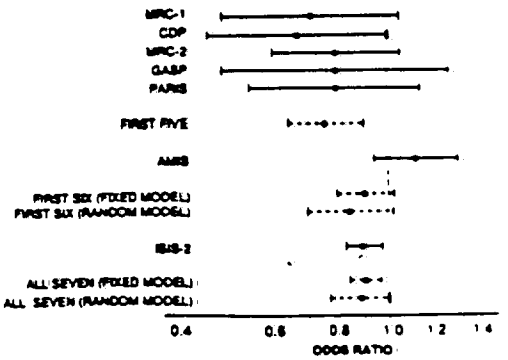

Fig. 1. Odds ratios and 95% confidence intervals for seven randomized trials of the effectiveness of aspirin after myocardial infarction.

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limits. Important examples from overviews of clinical trials of the effectiveness of beta-blockers in reducing the risk of mortality after myocardial infarction have been provided by Baber and Lewis [31] and by Yusuf *et al.* [17]. Studies may be separated by the time during which they were carried out (early or late during the development of a treatment [31]), or by other characteristics of the trials.

Peto has proposed an alternate method for the graphical presentation of the individual studies' results [32], one that is less intuitively understandable but that lends itself more directly to sophisticated statistical analysis. For each study, the values of two statistics are calculated. One is the difference, $O-E$, between the observed number of treated patients who experienced the outcome event, O, and the number expected to have done so under the hypothesis that the treatment is no different from the control, E. The second statistic, V, is the variance of the difference $O-E$.

With the ordinate of a pair of ordinary rectangular axes representing $O-E$ and the abscissa representing V, each study is represented by a point. If a straight line passing through or near the origin provides an adequate fit to these points, the meta-analyst may conclude that the studies' odds ratios are approximately equal, with their average value estimable, roughly, as the antilogarithm of the slope of that line. A more precise estimator of the summary odds ratio is

$$\mathrm{OR} = \exp\left(\frac{\Sigma(O-E)}{\Sigma V}\right),$$

the antilogarithm of the ratio of the sum of all the $O-E$ values to the sum of all the V values. (When OR is outside of the interval from 0.2 to 5.0, this formula may be inaccurate [33], and should be replaced by the more accurate formulas due to Mantel and Haenszel [34] or by those presented in the Appendix). The statistical significance of the estimated odds ratio may be tested by referring the quantity.

$$Z = \frac{\Sigma(O-E)}{\sqrt{\Sigma V}}$$

to the standard normal distribution and declaring the summary odds ratio to be statistically significant if Z is sufficiently large. The lower and upper limits of an approximate 95% confidence interval for the population odds ratio, finally, are given by

$$\exp\left(\frac{\Sigma(O-E) \pm 1.96\sqrt{\Sigma V}}{\Sigma V}\right).$$

The reader should note that the confidence interval so obtained is not symmetric about the point estimate.

Studies fixed vs studies random

A debate that is far from being resolved concerns the issue of how, if at all, interstudy differences in the magnitudes of the estimated treatment effects are to be taken into account in the meta-analysis. With only a limited number of exceptions [35], virtually all meta-analyses have ignored differences in estimated effects between studies (except to describe them qualitatively), and have used in the analysis only within-study measures of precision. Thus, as an example, if in one meta-analysis there are two published studies with ORs of 1.0 and 6.0, if in another there are two published studies with ORs of 2.0 and 3.0, and if all four values of V (the variance of the logarithm of the OR) are equal to 0.01, then in both studies the value of the pooled OR will be 2.45 and in both studies the approximate 95% confidence intervals extend from 2.13 to 2.81. No cognizance is taken of the obvious fact that the two studies in the first meta-analysis are much further apart than the two studies in the second. If each study were so large that the sampling variances were all equal to zero, both confidence intervals would degenerate to the single value of 2.45. The conclusion in both cases would be that the odds ratio was known with certainty to equal 2.45, although this cannot possibly be correct given that the individual ORs do not equal one another.

Peto, on the one hand, nevertheless asserts that this is precisely as things should be [36], whereas Meier, on the other, argues that interstudy variation is a key feature of the data and should contribute to the analysis [37]. In the jargon of the analysis of variance, Peto's perspective is that the studies represent levels of a *fixed factor* whereas Meier's is that they represent levels of a *random factor*. DeMets [26] and Bailey [38] discuss the pros and cons of these two competing statistical models, with Bailey presenting those circumstances, assumptions and research questions under which one or the other perspective is the more appropriate.

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Bailey [38] suggests that, when the research question concerns whether the treatment *will* have an effect, on the average, or whether exposure to a hypothesized risk factor *will* cause disease, on the average, then the model of studies being random is the appropriate one. When the question concerns whether treatment *has* produced an effect, on the average, or whether exposure *has* caused disease, on the average, *in the studies at hand*, then the model of studies being fixed is the appropriate one. The former question implicitly assumes that there is a population of studies from which those included in the meta-analysis were sampled. It anticipates the possibility of future studies being conducted, or even previously unknown studies being uncovered. The latter question assumes that only the studies included in the meta-analysis are of interest, and that there is no interest in generalizing the result to other studies. The former question, in our opinion, is usually the more important of the two.

In the first of the two hypothetical meta-analyses, the random effects model yields an approximate 95% confidence interval extending from below 0.5 to above 10.0. In the second, it yields an approximate 95% confidence interval extending from 1.65 to 3.64. These intervals were constructed using the method of Der Simonian and Laird [39] (see the Appendix). In our opinion, the difference between the two intervals based on the random effects model accurately reflects the difference that exists between the two pairs of studies, whereas the equality of the more traditional intervals based on the fixed effects model does not.

The potential for fragility in meta-analysis

It is possible for a single study to exert a powerful influence on the results of a meta-analysis. A striking example is provided by the meta-analysis of randomized trials of the effectiveness of aspirin in preventing death after a myocardial infarction [38]. Summary results are presented in Table 1 and in Fig. 1 for seven trials carried out between 1976 and 1988. The first five [40–44] constituted a homogeneous set (the value of the chi-square statistic for homogeneity of ORs was 0.62 with 4 *df*, far from statistical significance), for which the value of the summary OR for aspirin vs control was 0.76 (statistically significant at $p < 0.01$), with a 95% confidence interval extending from 0.65 to 0.90.

The next trial, the Aspirin Myocardial Infarction Study (AMIS) [45], changed the picture radically. Its OR of 1.13, while not significantly different from unity, was significantly different from the earlier pooled OR of 0.76 ($\chi^2 = 9.31$, $df = 1$, $p < 0.01$). The value of the summary OR across the first six studies was a statistically non-significant 0.90 ($p > 0.10$), with a 95% confidence interval extending from 0.80 to 1.02.

The confidence intervals for the first five studies and for the first six demonstrate the paradox discussed earlier that as one's uncertainty as to the value of the overall OR increases, the length of the confidence interval based on the fixed effects model decreases. The estimates and confidence intervals provided by the DerSimonian–Laird random effects model [39] for the six studies are more valid given the degree of heterogeneity that exists across them. The estimated odds ratio has a borderline significant value of 0.84 ($\chi^2 = 3.05$, $df = 1$, $p < 0.10$), and the associated 95% confidence interval extends from 0.70 to 1.02. The length of the DerSimonian–Laird interval is, in logarithmic units, ln (upper limit/lower limit) = ln (1.02/0.70) = 0.38, appropriately greater than both the length of the fixed effects interval for the first five studies (ln(0.90/0.65) = 0.32) and that for the first six (ln(1.02/0.80) = 0.24). (The fixed effects and random effects analyses of the first five studies yield identical results).

There were no obvious reasons for removing AMIS from the meta-analysis, other than the invalid one that its results differed significantly from those of the first five studies. The state of

Table 1. Results of seven placebo-controlled randomized studies of the effect of aspirin in preventing death after myocardial infarction

Study	No. deaths/No. patients		OR	$y = \ln(OR)$	$w = 1/\mathrm{Var}(y)$
	Aspirin	Placebo			
MRC-1 [40]	49/615	67/624	0.720	−0.329	25.710
CDP [41]	44/758	64/771	0.681	−0.384	24.291
MRC-2 [42]	102/832	126/850	0.803	−0.219	48.801
GASP [43]	32/317	38/309	0.801	−0.222	15.440
PARIS [44]	85/810	52/406	0.798	−0.226	28.409
AMIS [45]	246/2267	219/2257	1.133	0.125	103.985
ISIS-2 [46]	1570/8587	1720/8600	0.895	−0.111	663.923

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knowledge was therefore ambiguous: the first five studies collectively pointed to a statistically significant and fairly strong effect of aspirin for secondary prevention after a myocardial infarction, but the first six provided, at best, only suggestive evidence for the effectiveness of aspirin. This ambiguity was not resolved until the results of a seventh study, the Second International Study of Infarct Survival (ISIS-2) [46], were published. For the sake of comparability across all studies, the analyses below are based on the 2-year all-cause mortality rates from ISIS-2.

According to the DerSimonian–Laird random effects analysis, the overall OR across all seven studies was equal to a barely statistically significant 0.88 ($\chi^2 = 4.36$, $df = 1$, $p < 0.05$), with a 95% confidence interval extending from 0.77 to 0.99. The fixed effects analysis of these seven studies suggested (inappropriately, we believe) sharper conclusions: a highly significant point estimate for the OR of 0.90 ($\chi^2 = 10.6$, $df = 1$, $p < 0.005$), with a narrow 95% confidence interval extending from 0.84 to 0.96. We question the validity of the latter analysis because significant between-study variation remains (the OR for AMIS is not only significantly different from the average OR for the first five studies, as found before, it is significantly different from the OR for ISIS-2 ($\chi^2 = 4.95$, $df = 1$, $p < 0.05$)).

The overall substantive conclusion from this meta-analysis is that aspirin seems to be a modestly effective agent for reducing the risk of death during a period of approximately 2 years after a myocardial infarction, with a percentage reduction in the odds for dying relative to placebo equal to approximately 10%. The limits of uncertainty about this value are unsure, with the conservative random effects approach yielding a much wider confidence interval than the anticonservative fixed effects approach (in both instances, though, the upper confidence bound was less than 1.0).

The major methodological conclusion is that a single study may exert a powerful effect on one's conclusions. Here, there were two such influential studies. AMIS undid the statistically significant effect of aspirin found in the first five studies, and ISIS-2 undid the statistically non-significant effect of aspirin found in the first six. Given that one cannot know whether or when the next and potentially decisive study will be conducted, it would be prudent always to attach greater uncertainty than provided by traditional confidence intervals to the results of a meta-analysis of the studies conducted to date.

Execution and reporting

Several authors have proposed guidelines for carrying out and publishing the results of meta-analyses [3,16,47]. Although these guidelines are presented specifically for the meta-analysis of randomized clinical trials, they apply, with only minor exceptions, to meta-analyses in epidemiology as well. In our opinion, the standards and criteria offered by Sacks *et al.*[3], including, as they do, most of the others' guidelines, are the most useful. The six areas within which a meta-analysis should be evaluated, with those of their subdivisions that pertain to both clinical trials and epidemiology, follow:

(A) Study design. Just as the individual studies being meta-analyzed should be rigorously designed, with the design carefully and completely described, so should the meta-analysis itself. The meta-analysis should be carried out in accordance with a protocol prepared before the initiation of the study. The report of its results should describe the methods used by the meta-analysts to find all relevant articles, abstracts, chapters, etc.; should list the studies analyzed and enumerate those that were excluded (with reasons for their exclusion); and should provide summary data on the clinical and demographic characteristics of the subjects in the studies (subtypes of lung cancer, for example, in case–control studies).

(B) Combinability. The authors should address the statistical issue of whether the results from the separate studies should have been combined. If the estimates of treatment effect in clinical trials or of exposure–illness association in epidemiological studies differed significantly one from another, and especially if there was evidence of "qualitative interaction" (the estimates being in one direction in some studies and in the other direction in others), the authors should discuss why they proceeded to pool the results from all the studies.

(C) Control and measurement of potential bias. Several sources of unconscious bias exist, each of which should be addressed in the protocol for the meta-analysis. The more important ones would be discussed in the publication reporting on the results of the meta-analysis. Bias may occur in the decision as to which studies to select and which to exclude. Ideally, the decision should be made by one or more reviewers who

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concentrate on the study's methods and are kept blinded to the study's results.

Bias may exist in the process of extracting the summary estimates of effect or association from the publication of the study's results. This is especially likely to occur in epidemiological studies, in which many actual or potential confounding variables are controlled—separately or in combination—and in which many estimates of relative risk are produced. Depending on their predilections, reviewers might tend to choose the largest estimate, the smallest estimate, or, in order to be fair, the estimate closest to the average of the individual ones. A solution may be to have two or more reviewers carry out the data-extraction independently, and to resolve any disagreement by having them discuss the study and reach consensus.

Sacks and his colleagues recommend, finally, that the sources of support for the meta-analysis be identified.

(D) Statistical analysis. Depending on the nature of the response variable, quantitative or categorical, either an analysis of variance [24] or a variation of the Mantel–Haenszel procedure [34], both of which properly average within-study differences, should be employed. Point and interval estimation are desirable in addition to significance tests. If the meta-analysis fails to demonstrate a significant overall effect or association, the possibility of inadequate power should be considered. When specific effects or associations within subgroups were hypothesized *a priori*, separate meta-analyses should be performed within those subgroups.

(E) Sensitivity analysis. When possible, the studies' results should be analyzed in two or more ways in order to confirm that the final result from the meta-analysis is qualitatively the same no matter how the results are analyzed. The quality of the individual studies should be determined and incorporated into the final conclusions from the meta-analysis. The possible impact of publication bias and of the "file drawer problem" should be carefully considered.

(F) Application of results. Bringing to bear all of the above considerations, the meta-analysts should come to a decision as to whether the pooled results provide a definitive, effectively final answer to the research question, or whether the conclusions are tentative and further individual studies are needed.

III. APPLICATIONS OF META-ANALYSIS TO EPIDEMIOLOGICAL STUDIES OF EXPOSURE TO ETS AND LUNG CANCER

An important application of meta-analysis was the analysis by the National Research Council (NRC) [48] of all known epidemiological studies (through 1986) of the hypothesized association between a non-smoker's exposure at home to environmental tobacco smoke (ETS) and the risk of lung cancer. The overall OR found by the NRC was a statistically significant 1.34 ($p < 0.001$), with a 95% confidence interval extending from 1.18 to 1.53. Among the other criticisms of the NRC's meta-analysis that are to be addressed subsequently is the criticism that many biases in the individual studies that should have been accounted for were not.

Four studies were excluded from the NRC's meta-analysis, for apparently valid reasons: no reference population was given, no raw data were presented, etc. Aside from their specification of the reasons for the exclusion of these four studies, the authors of the NRC report appear not to have followed the major guidelines proposed by Sacks *et al.* [3]. For example, they did not provide a formal protocol for the meta-analysis, nor, apparently, did they give any consideration to the possibility of heterogeneous ORs across the several studies.

In addition, most of the decision points and sources of bias discussed in Section II in connection with the meta-analysis of clinical trials also apply to the meta-analysis of epidemiological studies. For example, studies that fail to show an effect of treatment are often not published either due to a "publication bias," i.e. articles that fail to show an effect of treatment are often rejected for publication, or due to the "file drawer phenomenon," i.e. there is a tendency on the authors' part not to submit for publication an article that fails to show an effect. These two related sources of bias are clearly present in epidemiological studies as well as in clinical trials. For example, it may be that a study comparing the incidence of lung cancer among non-smokers exposed to ETS against the incidence of lung cancer among non-smokers not so exposed yielded a relative risk substantially less than one. The world of science, as it is today, might well preclude the publication of such a study [49].

Furthermore, the question comes to mind whether the existing epidemiological studies of a possible association between exposure to ETS and the incidence of lung cancer in non-smokers

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are of adequate quality. Indeed, there is the question whether any of these studies meets even minimal standards of quality [50, 51].

Letzel *et al.* [51] considered the effects of misclassification errors on the results of the NRC's meta-analysis. They assumed three sets of conservative rates of misclassification for both disease and exposure to ETS, and, after adjusting for misclassification, concluded that "taking all this evidence together our calculations show that the findings of all studies about female lung cancer from passive smoking are consistent with the null hypothesis." Their final statement, also worth quoting, reads: "This brings us to final conclusion that there are presently only 2 alternatives—accepting the null hypothesis or creating new empirical evidence by peforming a really good study."

We shall nevertheless meta-analyze the nine American epidemiological studies that have, to our knowledge, been performed, the five that were included in the NRC report [48] plus four more recent ones. It is important to remind ourselves beforehand that there are many biases and confounders that will tend to inflate the relative risk. An especially important one is the misclassification of actual smokers as non-smokers. As Lee [52, 53] and Letzel *et al.* [51] point out, a woman who claims to be a non-smoker is more likely to be or to have been an actual smoker if married to a smoker than if married to a non-smoker. Other sources of bias include the misclassification of disease (i.e. misclassifying a non-lung cancer patient as having lung cancer as the primary disease, and misclassifying a lung cancer patient as not having cancer [51]), differing lifestyles between households where tobacco is used and those where tobacco is not used, and differential exposure and duration of exposure to air pollution between the exposed and unexposed groups. These biases have been considered to varying degrees by researchers in the field, with generally little success in controlling them.

One major source of bias that has not been analyzed sufficiently thoroughly, and has not yet been adequately controlled, is the misclassification of the spouse's smoking history (in this discussion the spouse is the husband or wife of the patient or of the control). It is possible that a non-smoking woman with lung cancer will overestimate the amount or duration of her husband's smoking in an attempt to find a causal explanation for her disease. The same tendency might be expected to exist when it is a surrogate for the patient—a child or sibling, or the spouse himself—who is being asked to report on the spouse's smoking history. The latter point is important because the proportion of patients reported on by a surrogate exceeds 50% in some studies.

U.S. studies of ETS and lung cancer

There are many reasons for restricting attention to American studies of whether there is an elevated risk of lung cancer to non-smokers exposed to ETS relative to non-smokers not so exposed. One is that this is the population to whom policy decisions will apply and on whom those decisions should be based. Another is that the summary ORs in the individual studies are derived from distributions of smoking amounts and durations, and of brands of cigarettes and other tobacco products, that pertain to populations within the U.S., and may thus be expected to be relatively homogeneous. Odds ratios from studies in other countries, on the other hand, are derived from distributions that may differ markedly from those in the U.S., and thus the ORs themselves may not be relevant to the American experience. Genetic and lifestyle differences between the U.S. population and the populations studied elsewhere (mainly in east Asia) also argue for a meta-analysis only of U.S. studies.

The first U.S. study, by Garfinkel [54], was a prospective follow-up study of more than 175,000 women who reported themselves to be non-smokers. All types of cancer of the lung were taken as end points. A "non-smoker" in this study was not only a women who reported that she never smoked, but also one who reported that she smoked only occasionally but not regularly. Little if any attempt seems to have been made to verify these women's self-reports.

The remaining U.S. studies were all case–control studies comparing patients with lung cancer against one or another kind of comparison group. The first was the study in New Orleans by Correa *et al.* [55]. Controls were patients with other diseases, from the same hospitals as the lung cancer cases, who were matched to the cases on age, sex and race. Specially trained interviewers were relied on to obtain exposure data for the cases and controls, although it is not clear whether the interviewers were blinded to whether a patient was a case or a control. The next of kin served as a proxy for the patient in 24% of the cases and 11% of the controls.

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In the study by Kabat and Wynder [56], lung cancer patients in six cities were identified, and controls were matched to the cases on age, sex, race, date of interview and hospital. More care seems to have been taken in this study than in the others to ensure that subjects classified as non-smokers were truly such. Interviewers used a standardized questionnaire, but it is unclear whether they were blinded to the status of the patient as a case or a control.

The study of Buffler *et al.* [57] was conducted in six coastal counties in Texas. Little information is provided about such key features of the study as the criteria for classifying the spouse as a "regular smoker" or not, whether ex-smokers were included or excluded, whether the interviewers were blinded, and the number of patients for whom a surrogate interviewer was required.

Garfinkel *et al.* [58] studied cases and controls from hospitals in New Jersey and Ohio. Controls were patients with colorectal cancer, matched to the cases on age and hospital. The interviewers were kept blinded to the status of each patient. Women were counted as unexposed to ETS even if their husbands smoked cigarettes "only occasionally." There was extensive reliance on surrogate interviewees, many with questionable knowledge about the patient: approximately one quarter of all interviews were with someone other than the patient, the spouse or a child, about 60% were with the spouse or a child, and only 12% were with the patient herself.

The case–control study by Wu *et al.* [59], conducted in Los Angeles County, was the first to use neighborhood rather than hospital-ized controls. Only cases who were still alive were interviewed (all on the telephone); i.e. no surrogates were permitted for cases who had died or who refused to be interviewed. No information was provided as to whether the interviewers were blinded. The point estimate of the OR given by the authors in their paper's abstract and in the text on p. 748, OR = 1.2, is inconsistent with the confidence interval reported in both of those places, 0.5–3.3 (the geometric mean of the limits must equal the point estimate). Instead of working with these incorrect values, we used in Table 2 and in Fig. 2 of this paper the values for "spouse smoked" for adenocarcinoma in their Table 2: OR = 1.2, with a 95% confidence interval extending from 0.6 to 2.5.

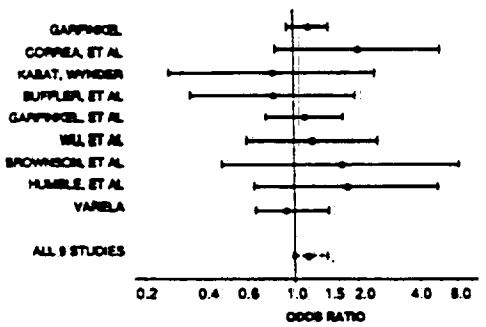

Fig. 2. Odds ratios and 95% confidence intervals for nine U.S. epidemiological studies of the hypothesized association between exposure to environmental tobacco smoke and lung cancer.

Table 2. Summary results of U.S. epidemiologic studies of the association between a non-smoking woman's exposure to environmental tobacco smoke and the risk of lung cancer

Study	OR	$y = \ln(OR)$	$w = 1/\mathrm{Var}(y)$
Garfinkel [54]	1.17	0.157	73.730
Correa *et al.* [55]	2.02	0.703	4.745
Kabat and Wynder [56]	0.79	−0.233	3.061
Buffler *et al.* [57]	0.80	−0.226	4.777
Garfinkel *et al.* [58]	1.12	0.113	22.330
Wu *et al.* [59]	1.22	0.199	7.545
Brownson *et al.* [60]	1.68	0.519	2.310*
Humble *et al.* [61]	1.78	0.577	3.826
Varela [62]	0.91	−0.090	36.268

*From personal communication from Dr Brownson.

Brownson *et al.* [60] carried out their case–control study in Denver. The controls were patients with cancer of the colon or bone marrow and were matched according to age and sex (there was approximately a 50:50 split on sex for the patients with lung cancer). The interviewer was blinded to the case or control status of the patient. The interviewee was someone other than the patient (mainly the spouse but occasionally a sibling or child) for nearly 70% of the cases and almost 40% of the controls. Exposure to ETS was not dichotomized in their Table 4 as "none" vs "any" but as "less than four hours per day" vs "four or more". The 95% confidence interval for the OR there should extend from 0.46 to 6.10 (personal communication from the senior author).

The study by Humble *et al.* [61] was a population-based case–control study in New Mexico. Controls were obtained by random digit dialing or from a randomly generated list of Medicare recipients. They were selected to match the frequency distributions of the cases on sex, ethnicity and age. The patient's status as a never-smoker was checked against the information recorded in the hospital chart. More than half of the time a surrogate was relied on

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for exposure information about the case. It is unclear whether the interviewers were kept ignorant of the subject's status.

Varela's study [62] was carried out in New York State, with the controls being selected from State motor vehicle records. They were matched to the cases on age, sex, county of residence and previous smoking history. The questionnaire administered to the cases was slightly different from the one administered to the controls, so blinding was obviously impossible. Surrogate interviewees were permitted for the one-third of cases who had died or could not be interviewed for other reasons, but in such instances a surrogate respondent was interviewed for the matched control.

A final publication pertaining to experience in the U.S. is by Dalager *et al.* [63]. Rather than being a report on a new study, this paper reports the results of a summarization of data reported on earlier by Correa *et al.* [55] and by Buffler *et al.* [57], plus data that apparently have not yet been published anywhere. The results of the analysis may not be totally valid because "the data from all three study areas were merged" instead of being combined using the methods described in the Appendix. In any event, to have included the results of the quasi-meta-analysis by Dalager *et al.* [63] in our meta-analysis would have resulted in the studies by Correa *et al.* [55] and Buffler *et al.* [57] inappropriately being counted twice.

The overall quality of the American studies is obviously quite variable, just as it is for all such studies world-wide. Because we did not develop *a priori* a set of procedures for the unbiased measurement of a study's quality, it is appropriate that we include all known U.S. studies in our meta-analysis [54–62]. Most of these studies reported several values for the odds ratio. We selected for analysis one value per study, the value we believe the authors took to be their most accurate measure of association between exposure to ETS and lung cancer. These usually agreed with the values selected by the NRC [48] and by Layard [50] in their meta-analyses.

The results are presented in Table 2 and Fig. 2. There is no evidence for study-to-study heterogeneity (the value of the chi-square statistic with 8 *df* is a non-significant 5.46). The OR of 1.17 for the single prospective study, that by Garfinkel for the American Cancer Society [54], is close in value to the average OR of 1.07 for the eight case–control studies [55–62]. The overall OR across all nine studies is equal to a statistically non-significant 1.12 ($\chi^2 = 1.88$, $df = 1$), with the 95% confidence interval extending from 0.95 to 1.30. The fact that no significant association was found neither vindicates nor condemns the meta-analysis of these epidemiological studies. Given the biases that exist in each individual study, the safest conclusion from the present meta-analysis is a negative one: there is no convincing scientific evidence from the epidemiological literature of an association between exposure to ETS and the risk of lung cancer in the U.S.

IV. CONCLUSIONS

Meta-analyses, when properly performed, can be used effectively in both clinical trials and epidemiological studies for the following purposes:

- To increase the power of statistical tests for important endpoints and subgroups.
- To make sense out of studies with conflicting conclusions.
- To improve estimates of effect size.

However, uncritical use of meta-analysis can and does lead to unsubstantiated conclusions. Only when all the issues that we have discussed are considered and properly accounted for is it possible to apply meta-analysis to combine studies so that the overall result is scientifically valid. These issues include publication bias, the question of heterogeneity across studies, whether all subjects should be included in the meta-analysis or only those who are compliant with their treatment (this pertains only to clinical trials), whether proper control or adjustments have been made in epidemiological studies for sociodemographic or clinical differences between study populations, and the possible misclassification of subjects with regard to levels of exposure and case–control status.

It is very unlikely that the biases present in the epidemiological studies of the possible association between exposure to ETS and the risk of lung cancer can ever be removed. The meta-analysis performed by the NRC [48] must either be completely discounted or, as Stein [23] concluded so succinctly in another context, considered a mere "computational exercise."

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REFERENCES

1. Huque MF. Experiences with meta-analysis in NDA submissions. **Proc Biopharmaceutical Section of the American Statistical Association** 1988; 28–33.
2. Hedges LV, Olkin I. **Statistical Methods for Meta-analysis.** New York: Academic Press; 1985.
3. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analysis of randomized controlled trials. **N Engl J Med** 1987; 316: 450–455.
4. Chalmers TC, Levin H, Sacks HS, Reitman D, Berrier J, Nagalingam R. Meta-analysis of clinical trials as a scientific discipline. I. Control of bias and comparison with large co-operative trials. **Stat Med** 1987; 6: 315–325.
5. O'Rourke K, Detsky AS. Meta-analysis in medical research: Strong encouragement for higher quality individual research efforts. **J Clin Epidemiol** 1989; 42: 1021–1029.
6. Peto R. Why do we need overviews of randomized trials. **Stat Med** 1987; 6: 233–240.
7. Pocock SJ. **Clinical Trials: A Practical Approach.** New York: Wiley; 1983: 244.
8. Yusuf S. Obtaining medically meaningful answers from an overview of randomized clinical trials. **Stat Med** 1987; 6: 281–286.
9. Gehan EA, Freireich EJ. Non-randomized controls in cancer clinlical trials. **N Engl J Med** 1974; 290: 198–203.
10. Light RJ. Accumulating evidence from independent studies: What we can win and what we can lose. **Stat Med** 1987; 6: 221–228.
11. Hedges LV. Commentary. **Stat Med** 1987; 6: 381–385.
12. Eysenck HJ. An exercise in mega-silliness. **Am Psychol** 1978; 33: 517.
13. Chalmers TC, Smith H Jr, Blackburn B, Silverman B, Schroeder B, Reitman D, Ambroz A. A method for assessing the quality of a randomized control trial. **Contr Clin Trials** 1981; 2: 31–49.
14. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. **Am J Epidemiol** 1990; 142: 612–628.
15. Glass GV, McGass B, Smith ML. Meta analysis in social research. Beverly Hills, Calif.: Sage; 1981: 220–226.
16. Jenicek M. Meta-analysis in medicine: Where we are and where we want to go. **J Clin Epidemiol** 1989; 42: 35–44.
17. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction. An overview of the randomized trials. **Prog Cardiovasc Dis** 1985; 27: 335–371.
18. Smith M, Glass G, Miller T. **The Benefits of Psychotherapy.** Baltimore: Johns Hopkins University Press; 1980.
19. Rosenthal R. The "file drawer problem" and tolerance for null results. **Psychol Bull** 1979; 86: 638–641.
20. Iyengar S, Greenhouse JB. Selection models and the file drawer problem. **Stat Sci** 1988; 3: 109–117.
21. Berlin JA, Begg CB, Louis TA. An assessment of publication bias using a sample of published clinical trials. **J Am Stat Assoc** 1989; 84: 381–392.
22. Dubey S. Regulatory considerations on meta-analysis, dentifrice studies and multicenter trials. **Proc Biopharmaceutical Section of the American Statistical Association** 1988; 18–27.
23. Stein RA. Meta-analysis from one FDA reviewer's perspective. **Proc Biopharmaceutical Section of the American Statistical Association** 1988; 34–38.
24. Fleiss JL. **The Design and Analysis of Clinical Experiments.** New York: Wiley; 1986: 176–180.
25. Fleiss JL. **Statistical Methods for Rates and Proportions,** 2nd edn. New York: Wiley; 1981: 161–164.
26. DeMets DL. Methods for combining randomized clinical trials: Strengths and limitations. **Stat Med** 1987; 6: 341–348.
27. Stampfer MJ, Goldhaber SZ, Yusuf S, Peto R, Hennekens CH. Effect of intravenous streptokinase on acute myocardial infarction. Pooled results from randomized trials. **N Engl J Med** 1982; 307: 1180–1182.
28. Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. **N Engl J Med** 1988; 318: 385–392.
29. Friedman LM, Furberg CD, DeMets DL. **Fundamentals of Clinical Trials,** 2nd edn. Littleton, Mass.: PSG Publishing; 1985: 246–249.
30. Sackett DL, Gent M. Controversy in counting and attributing events in clinical trials. **N Engl J Med** 1979; 301: 1410–1412.
31. Baber NS, Lewis JA. Confidence in results of beta-blockers post-infarction trials. **Br Med J** 1982; 284: 1749–1750.
32. Peto R. Discussion of DeMets DL. Methods for combining randomized clinical trials: Strengths and limitations. **Stat Med** 1987; 6: 349–350.
33. Greenland S, Salvan A. Bias in the one-step method for pooling study results. **Stat Med** 1990; 9: 247–252.
34. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. **J Natl Cancer Inst** 1959; 22: 719–748.
35. Hine L, Laird NM, Hewitt P, Chalmers TC. Meta-analysis of empirical long-term anti-arrhythmic therapy after myocardial infarction. **JAMA** 1989; 262: 3037–3040.
36. Peto R. Discussion of Peto R. Why do we need systematic overviews of randomized trials? **Stat Med** 1987; 6: 242.
37. Meier P. Commentary. **Stat Med** 1987; 6: 329–331.
38. Bailey KR. Inter-study differences: How should they influence the interpretation and analysis of results? **Stat Med** 1987; 6: 351–358.
39. DeSimonian R, Laird N. Meta-analysis in clinical trials. **Contr Clin Trials** 1986; 7: 177–188.
40. Elwood PC, Cochrane AL, Burr ML, Sweetnam PM, Williams G, Welsby E, Hughes SJ, Renton R. A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. **Br Med J** 1974; 1: 436–440.
41. Coronary Drug Project Group. Aspirin in coronary heart disease. **J Chron Dis** 1976; 29: 625–642.
42. Elwood PC, Sweetnam PM. Aspirin and secondary mortality after myocardial infarction. **Lancet** 1979; 2: 1313–1315.
43. Breddin K, Loew D, Lechner K, Uberla EW. Secondary prevention of myocardial infarction. Comparison of acetylsalicylic acid, phenprocoumon and placebo. A multicenter two-year prospective study. **Thromb Haemost** 1979; 41: 225–236.
44. Persantine–Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. **Circulation** 1980; 62: 449–461.
45. Aspirin Myocardial Infarction Study Research Group. A randomized controlled trial of aspirin in persons recovered from myocardial infarction. **JAMA** 1980; 243: 661–669.
46. ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. **Lancet** 1988; 2: 349–360.
47. Meinert CL. Meta-analysis: Science or religion? **Contr Clin Trials** 1989; 10: 257S–263S.
48. National Research Council. **Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.** Washington: National Academy Press; 1986.

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49. Vandenbrouke JP. Passive smoking and lung cancer: A publication bias? **Br Med J** 1988; 296: 391–392.
50. Layard MW. Environmental tobacco smoke and cancer: The epidemiologic evidence. In: Ecobichon DJ, Wu JM, Eds. **Environmental Tobacco Smoke: Proc Int Symp**, McGill University, 1989. Lexington, Mass.: Lexington Books; 1990: 99–115.
51. Letzel H, Blumner E, Uberla K. Meta-analyses on passive smoking and lung cancer: Effects of study selection and misclassification of exposure. **Environ Technol Lett** 1988; 9: 491–500.
52. Lee PN. Lung cancer and passive smoking. **Toxicol Lett** 1987; 35: 157–162.
53. Lee PN, Chamberlain J, Alderson MR. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. **Br J Cancer** 1986; 54: 97–105.
54. Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. **J Natl Cancer Inst** 1981; 66: 1061–1066.
55. Correa P, Pickle LW, Fontham E, Lin Y, Haenszel W. Passive smoking and lung cancer. **Lancet** 1983; 2: 595–597.
56. Kabat GC, Wynder EL. Lung cancer in nonsmokers. **Cancer** 1984; 53: 1214–1221.
57. Buffler PA, Pickle LW, Mason TJ, Contant C. The causes of lung cancer in Texas. In: Mizell M, Correa P, Eds. **Lung Cancer: Causes and Prevention**. New York: Verlag-Chemie International; 1984: 83–99.
58. Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: A case-control study. **J Natl Cancer Inst** 1985; 75: 463–469.
59. Wu AH, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. **J Natl Cancer Inst** 1985; 74: 747–751.
60. Brownson RC, Reif JS, Keefe TJ, Ferguson SW, Pritzl JA. Risk factors for adenocarcinoma of the lung. **Am J Epidemiol** 1987; 125: 25–34.
61. Humble CG, Samet JM, Pathak DR. Marriage to a smoker and lung cancer risk. **Am J Publ Health** 1987; 77: 598–602.
62. Varela LR. Assessment of the association between passive smoking and lung cancer. PhD dissertation. Yale University; 1987.
63. Dalager NA, Pickle LW, Mason TJ, Correa P, Fontham E, Stemhagen A, Buffler PA, Ziegler RG, Fraumeni JF. The relation of passive smoking to lung cancer. **Cancer Res** 1986; 46: 4808–4811.

APPENDIX

Statistical Appendix: Analysis of Log Odds Ratios

Suppose that there are, all told, S studies to be meta-analyzed. In a typical one, say study s, let n_{s1} and n_{s2} be the sample sizes in the two groups being compared and let p_{s1} and p_{s2} be the proportions having the characteristic under study. In a randomized controlled trial the two groups would be the treated and placebo samples and the characteristic under study might relapse or some other kind of failure. In an epidemiological case–control study the two groups would be the cases and controls and the characteristic under study would be exposure to the hypothesized risk factor. A review of the fixed effects analysis of the data follows.

The logarithm of the OR in study s, denoted by y_s, equal to

$$y_s = \ln(p_{s1}(1 - p_{s2})/p_{s2}(1 - p_{s1})),$$

where ln denotes natural logarithm. The standard error of y_s is given by

$$\text{se}_s = \left(\frac{1}{n_{s1}p_{s1}(1 - p_{s1})} + \frac{1}{n_{s2}p_{s2}(1 - p_{s2})}\right)^{1/2},$$

and the factor by which y_s is weighted in the classical fixed effects analysis, w_s, is

$$w_s = 1/(\text{se}_s)^2.$$

The overall OR across all S studies is equal to

$$\overline{\text{OR}} = \exp(\bar{y}),$$

where $\bar{y} = \Sigma w_s y_s / \Sigma w_s$, and the limits of a 95% confidence interval for the overall OR are given by

$$\exp(\bar{y} \pm 1.96/\sqrt{\Sigma w_s}).$$

This interval will not be symmetric about $\overline{\text{OR}}$.

The "combinability" of the S studies, i.e. the hypothesis that the S underlying ORs are equal, may be tested by referring the statistic

$$Q = \Sigma w_s (y_s - \bar{y})^2$$

to percentage points of the chi-square distribution with $S - 1$ *df*. This same statistic Q plays a central role in the DerSimonian–Laird random effects analysis of the data [39]. In particular, the DerSimonian–Laird analysis is identical to the fixed effects analysis just presented if $Q \leqq S - 1$, but the two methods diverge if $Q > S - 1$.

Assume, therefore, the $Q > S - 1$, and define

$$D = \frac{(Q - (S - 1))\Sigma w_s}{(\Sigma w_s)^2 - \Sigma w_s^2}.$$

The DerSimonian–Laird weighting factor for study s is equal to

$$w_s^* = \left(D + \frac{1}{w_s}\right)^{-1},$$

and the random effects point and interval estimates of the overall OR become

$$\exp(\bar{y}^*)$$

and

$$\exp(\bar{y}^* \pm 1.96/\sqrt{\Sigma w_s^*}),$$

where $\bar{y}^* = \Sigma w_s^* y_s / \Sigma w_s^*$.

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Editorial

META-META-ANALYSIS: UNANSWERED QUESTIONS ABOUT AGGREGATING DATA

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Some days I ask myself if investigators still do their own trials, with admissible standards and adequate power. It seems like the most frequent prelude to a discussion on efficacy or safety of an intervention is, "... We did a meta-analysis of studies on ...". Does anyone do straightforward unhyphenated analyses any more?

In this issue of the **Journal** (pp. 127–139), Fleiss and Gross review and reassess meta-analysis and report an illustrative case study of the method focusing on the association between exposure to environmental tobacco smoke (ETS) and lung cancer. The article refers to a succinct and useful definition of meta-analysis offered by Huque [1] "... a statistical analysis which combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable'". I also take Huque's characterization as the working definition for this editorial comment and join Fleiss and Gross in highlighting the fact that meta-analysis' key and almost exclusive application to date has been in the integration of data from clinical trials. I would add that a distinctive characteristic of the strategy is the derivation of a single quantitative estimate of effect of an intervention or a risk factor. Fleiss and Gross touch on most of the main issues, including consensus and controversy. I will not repeat or summarize their elegant review which enumerates many of the unanswered questions about meta-analysis of experimental trials. But it deserves emphasis that the main unresolved challenges are to settle on universal widely acceptable criteria for exclusion of trials and the development of a reproducible, valid and accepted weighting index that would enable analysts to invoke the quality of the research into a final result. I will confine my comments mostly to the application of meta-analysis in aggregation of non-experimental (observational) studies. The controversies surrounding meta-analysis of experimental trials are equally relevant to non-experimental studies which are usually epidemiological. But there are additional unanswered questions. Fleiss and Gross ask, "... can meta-analytic techniques be applied in the analysis of other kinds of data such as those that arise in cohort and case–control studies found in epidemiology? Their answer is a "guarded 'yes'". I do not know whether the question can be answered at all. The illustrative meta-analytic project reported by them goes a long way in avoiding potential pitfalls. However, some problems are not fully addressed either in the execution of the study nor in the discussion about such applications in conventional epidemiology. There are many difficulties that have not been surmounted yet, either theoretically or empirically. When phrasing the following 13 unanswered questions, I have used words such as "merge", "combine", "integrate" or "put together", in respect to data from different case series, different series of reference groups, different cohorts, etc. I have done so recognizing that one usually

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combines intrastudy *differences*, not intrastudy disease or exposure rates. I ask the reader's indulgence for having avoided repetitive dense statistical technical terminology in deference to readable English prose. These then, are the questions:

(1) Operationally, what are the "stringent conditions" (Fleiss and Gross' phrase) under which both case–control studies and cohort studies may be included in one single meta-analysis? Should such analyses ever be done without access to the raw data of the component studies?

(2) When is it permissible to combine different types of cohort? For instance, for both exposed cohorts and comparison cohorts should one integrate data from a fixed cohort with an open one?

(3) Is it permissible to integrate exposed patients sampled from hospitals with those from primary care settings?

(4) For reference cohorts, *not exposed* to an intervention or risk factor, other questions arise. For example,

  (a) Is a comparison cohort from Sweden combinable with one from Italy or Japan?

  (b) Are cohorts taken from occupational sampling frames sufficiently similar to those from the corresponding general population (or another geographically-defined one) to put them together?

  (c) How separate in time must the accrual or demarcation of unexposed cohorts become to be ineligible for aggregation? (The question is also pertinent for exposed cohorts.)

Turning now to case–control designs:

(5) Is it admissible to merge hospital-based with population-based case groups? Or in Miettinen's terms, can two or more case series be combined if they are not representative of the same type of base experience? [2].

(6) Conceptually, and in execution, is a nested case–control study similar enough to a conventional case–control study for both to be included in the same meta-analysis?

(7) When there are two or more control groups in a case–control study does one merge all the control groups? If not, what criteria must one use to exclude any control group from the meta-analysis? There is no parallel between multiple arms defined by exposure in a randomized controlled trial and multiple reference samples demarcated by outcome in a case–control study.

(8) Should control groups assembled by matching be combined with independent samples of referenced populations?

(9) What constitutes "proper control or adjustment for the biases that frequently occur in epidemiological studies?" [3]. Case–control studies are the designs in common use most vulnerable to bias [4]. I believe that the difficulties in minimizing bias acceptably, alone, could vitiate the validity of meta-analyses of case–control studies. Bias is barely manageable (and seldom managed well) even in single case–control studies. As pointed out by Fleiss and Gross [3], as well as Letzl earlier [5], misclassification bias for exposure is a particularly thorny problem.

(10) Are data provided by proxy informants similar enough to data from respondents to be considered equivalent?

(11) Should one include case–control studies in which data-gatherers were unblinded with blinded studies in one meta-analysis? (Should one do so in cohort research?)

(12) How homogeneous must the outcome be? For instance, can one pool data from a study that ascertained "all cancers of the lung", with one that did so only for "oat cell Ca", or only "adenocarcinoma"?

(13) How do we interpret values and confidence intervals of single estimates derived with meta-analysis? Consider a report of a single study comparing two fixed cohorts of 2500 persons. The relative risk (RR) for the association of the putative risk factor with the incidence of a well-defined, hard, but relatively uncommon outcome is 1.45. The 95% confidence interval is 1.02–2.07 and $p = 0.04$. In a hypothetical meta-analysis of five other follow-up studies with 500 persons per cohort (two in each study assessing the same risk factor and outcome) the result is an identical relative risk, the same confidence interval and an

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identical p value. In the second scenario the relative risks for the five component studies were 3.0 ($p = 0.013$), 0.6 ($p = 0.48$), 1.1 ($p = 0.80$), 1.5 ($p = 0.15$), 1.1 ($p = 0.83$). Do both sets of statistics mean the same thing? I remind the reader that it is not standard practice to incorporate interstudy variation with one's meta-analysis. Should one do so? Beyond problems of multiple comparisons which we usually recognize and correct, might there be a problem of "multiple combinations"?

As summarized by Fleiss and Gross, the indications for a properly conducted meta-analysis are,

(a) to increase statistical power,
(b) to deal with controversy when individual studies disagree,
(c) to improve estimates of size of effect and
(d) to answer new questions not previously posed in component studies [3]. But is it always necessary, or justified, to pursue a single estimate with its related probability qualifiers to derive conclusions from a series of research projects?

An alternative to both meta-analysis on one hand, and traditional (often haphazard) reviews is an approach proposed by Slavin and designated *best-evidence synthesis*. This approach considers that the "best evidence" in any field comes from studies having the highest internal and external validity, that use well-specified, defined, explicit *a priori* inclusion and exclusion criteria and favour size-effect data to statistical significance alone when interpreting the literature reviewed. Such syntheses emphasize numeric findings but the conclusions need not depend on a single estimation nor on statistical significance [6]. In common with properly executed meta-analyses best-evidence syntheses cannot evade the difficult challenge of deciding what to exclude and how to document the exclusions. Getting around "publication bias" [7] which means finding and judging unpublished work is particularly daunting.

What is attractive about best-evidence synthesis is that it liberates the analyst from the apparent obsession which meta-analysts have to calculate a single estimate as a necessary intermediate step to reach an opinion about an association, an effect or a casual relationship. Nevertheless, best-evidence synthesis does not exonerate the analyst from the highest attainable rigour in setting forth a protocol for the synthesis in advance. The protocol must then be followed when deciding which component studies reach a predetermined level of scientific admissibility, in establishing exclusion criteria, when implementing methods to document excluded research, when developing valid weighting schemes for the quality of papers, and when formulating predetermined explicit rules for judging effect size. The foregoing list of specifications for a best-evidence synthesis protocol is not exhaustive. I am of the opinion that even more rigour is required of the meta-analyst.

Turning now to Fleiss and Gross' illustrative case study that re-examines the association between exposure to environmental tobacco smoke and lung cancer [3], I shall highlight some of its features:

(i) They excluded non-American studies, a sensible move, given the unresolved methodological problems of pooling people of very different ethnic nature and of different culturally-determined views of smoking. The exclusion is particularly appropriate if the intention was to make inferences chiefly about the American population.
(ii) The meta-analysis incorporates one cohort study and eight case–control studies.
(iii) Hospital-based and population-based groups (both cases and controls) appear to have been considered equivalent. It is probably valid to have done so *when the purpose was to test the null hypothesis* of no association. Were one to attempt non-null inferences, it would have been a mistake to consider them equivalent.
(iv) Matched and unmatched controls were incorporated in a similar way.
(v) The overall analysis does not seem to have been adjusted by blindness status of data-gatherers nor by the extent that proxies or respondents provided information on exposure.
(vi) Outcomes were somewhat heterogeneous. Consequently, matched groups might have been different.

Lastly, they report,

(vii) "... we did not develop *a priori*, a set of procedures for the unbiased measurement of a study's quality ...".

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The seven comments are not made to rebuke Fleiss and Gross' approach but to underscore the enormous difficulties that they and anyone else unavoidably confront attempting a meta-analysis of non-experimental epidemiological studies.

The single estimate they report for the nine studies is 1.12 (CI 95% 0.95–1.30), $\chi^2 = 1.88$ (1 *df*). I consider the result and the resulting conclusion plausible and I completely agree with their comment. "The fact that no significant association was found neither vindicates nor condemns the meta-analysis of epidemiological studies" [3].

My colleagues and I, in a Working Group on Passive Smoking that reported early last year [8], also examined the association between exposure to environmental tobacco smoke (ETS) and lung cancer. We used Slavin's method of best-evidence synthesis rather than meta-analysis. We also included the world literature, not just U.S. studies. It is instructive to compare the two sets of conclusions on the association:

Fleiss and Gross: "... there is no convincing scientific evidence from the epidemiologic literature of an association between exposure to ETS and the risk of lung cancer in the United States" [3].

Spitzer et al.: "The weight of evidence is compatible with a positive association between residential exposure to environmental tobacco smoke (primarily from spousal smoking) and the risk of lung cancer". "There is no evidence for an association between non-residential exposure to ETS and any form of cancer" [8].

The two conclusions are not identical. But they are not directly contradictory nor mutually exclusive. Moreover, given the restriction of the meta-analysis to U.S. studies and the inclusion of admissible studies from anywhere in the world for the best-evidence synthesis the compatibility of the "verdicts" tends to mutually buttress their validity. Admittedly, the language of the discussion of the Fleiss and Gross paper [3] favours a *non-association* interpretation while the Spitzer group's comments do the opposite [8]. For example, contrast these phrases: "... the safest conclusion from the present meta-analysis is a negative one" [3]; "The preponderance of positive studies is consistent with a causal relationship betwen exposure to ETS and lung cancer" [8]. But it is obvious that there is a lot of common ground between the conclusions of two different methodological approaches to the quantitative evidence available on the subject.

A more general conclusion of Fleiss and Gross is important: "Meta-analyses, when properly performed, can be used effectively in both clinical trials and epidemiological studies ...". In today's state of science I accept the conclusion guardedly and warily, *for clinical trials only* despite many unresolved controversies about what "properly performed" means in the method. In my opinion, however, the unanswered questions about meta-analysis in non-experimental epidemiological studies do not yet warrant widespread application except as methodological research. I view Fleiss and Gross' analysis as a courageous, honest, trailblazing early step in the development of the method. Their own caveats throughout their article lend support to my opinion and to their scientific integrity.

In the near future we need a level of international consensus about the methods of meta-analysis as high as that which prevails for unmeta-analyzed single randomized controlled trials. Perhaps a "summit" should be called for. I would find it difficult to ignore a general agreement on criteria for scientific admissibility of meta-analytic studies (both clinical trials and non-experimental studies) if it were endorsed by a group including, say, Armitage, Breslow, Cole, Day, Detsky, Gross, Feinstein, Fleiss, Meier, Miettinen, R. Peto, Sackett, Schwartz, Uberla, Vessey, Walter and Zelen. Minor miracles still happen occasionally.

Finally, let's abolish the verb "to meta-analyze" as a substitute for "to review", "to synthesize", "to interpret" or even "to read". Careless use of the technically-specific term does not do justice to the unfulfilled promise of meta-analysis, nor to the painstaking work of many colleagues who pursue excellence as they attempt to deliver the promise.

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REFERENCES

1. Huque MF. Experiences with meta-analysis in NDA submissions. Proc Biopharmaceutical Section of the American Statistical Association 1988; 2: 28–33.
2. Miettinen OS. The "case-control" study: valid selection of subjects. J Chron Dis 1985; 38: 543–548.
3. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke

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and lung cancer: a critique. J Clin Epidemiol 1991; 44: 127–139.

4. Ibrahim MA, Spitzer WO, Eds. The case–control study: consensus and controversy. J Chron Dis 1979; 32: 1–90.
5. Letzel H, Blummer E, Uberla K. Meta-analyses on passive smoking and lung cancer: Effects of study selection and misclassification of exposure. Environ Technol Lett 1988; 9: 491–500.
6. Slavin RE. Best-evidence synthesis: an alternative to meta-analytic and tradiational reviews. Educ Res 1986; 15: 5–11.
7. Vandenbroucke JP. Passive smoking and lung cancer: a publication bias? Br Med J 1988; 296: 391–392.
8. Spitzer WO, Lawrence V, Dales R *et al*. Links between passive smoking and disease: A best-evidence synthesis. Clin Invest Med 1990; 13: 17–42.

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RISK ESTIMATES FOR NONSMOKER LUNG CANCER BASED UPON MODELING PROCEDURES

- In 1985, Repace and Lowrey published an article claiming that exposure to ETS is responsible for 500 to 5,000 lung cancer deaths per year in the United States.[1] This report received extensive press coverage upon its release.

- The report contains two highly theoretical models for estimating risks of lung cancer from ETS exposure. One model relies upon a "reinterpretation" of the epidemiologic studies of lung cancer in nonsmokers; the second model estimates lung cancer mortality among nonsmokers based on a single study dealing with the Seventh Day Adventists, a religious group known for its vigorous opposition to smoking.

- Critics of the Repace and Lowrey approach have pointed out that the estimates are based on errors and "unrealistic assumptions" which result in overestimations of exposure.[2] One analysis of the model showed that, depending on the assumptions and input data used, the estimates are inherently inaccurate and may vary by as much as 300-fold.[3] Another scientist noted that the exposure and dose levels used in the modeling exercise were not based on actual measurements; such measurements reported elsewhere range from "ten- to one-hundred-fold less than that in the Repace and Lowrey model."[4]

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- Other criticisms have focused on the report's methods of analysis,[5-7] and suggest that Repace and Lowrey failed to control for other confounding factors, and that their model did not provide "the very statistical bases of estimation procedures."[4]

- Repace and Lowrey's estimate of nonsmoker lung cancer risks in the workplace was also criticized by scientists who noted that none of the epidemiologic studies of ETS exposure and disease in nonsmoking working women report a statistically significant increase in risk.[2]

- Two British researchers, Darby and Pike, published a paper in 1988 describing another type of mathematical model which predicted potential effects from ETS exposure based on data from a study on active smoking.[8] Even when adjustments were made for childhood exposure to ETS, the authors reported that the model predicted a risk for nonsmokers that was smaller than "the underlying background risk for lung cancer." They concluded that their model could not explain the difference between risks reported for nonsmokers in epidemiologic studies and the low levels of ETS exposure reported in other studies.

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The Darby and Pike model was criticized in 1990 by Wald, et al., authors of one of the earlier meta-analyses on the epidemiologic studies of ETS exposure and lung cancer incidence.[9] Wald's group questioned Darby and Pike's conclusion that there was a discrepancy between risks estimated by epidemiologic studies and by exposure data. Darby and Pike replied that the existing cotinine data employed by Wald, et al., were possibly both insufficient and inappropriate to allow an adequate comparison to be made with the epidemiologic data.[10]

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REFERENCES

1. Repace, J.L. and Lowrey, A.H., "A Quantitative Estimate of Nonsmokers' Lung Cancer Risk from Passive Smoking," Environment International 11(1): 3-22, 1985.

2. Arundel, A., Irwin, T. and Sterling, T., "Nonsmoker Lung Cancer Risks from Tobacco Smoke Exposure: An Evaluation of Repace and Lowrey's Phenomenological Model," Journal of Environmental Science and Health C4(1): 93-118, 1986.

3. Arundel, A., Sterling, T. and Weinkam, J., "Never Smoker Lung Cancer Risks from Exposure to Particulate Tobacco Smoke," Environment International 13: 409-426, 1987.

4. Lebowitz, M.D., "The Potential Association of Lung Cancer with Passive Smoking," Environment International 12: 3-9, 1986.

5. Johnson, C. and Letzel, H., "Letter to the Editors," Environment International 12: 21-22, 1986.

6. Burch, P.R.J., "Health Risks of Passive Smoking: Problems of Interpretation," Environment International 12: 23-28, 1986.

7. Kilpatrick, S.J., "Letter to the Editors," Environment International 12: 29-31, 1986.

8. Darby, S.C. and Pike, M.C., "Lung Cancer and Passive Smoking: Predicted Effects from a Mathematical Model for Cigarette Smoking and Lung Cancer," British Journal of Cancer 58: 825-831, 1988.

9. Wald, N., Nanchahal, K., Cuckle, H. and Thompson, S., "Letter to the Editor: Lung Cancer and Passive Smoking," British Journal of Cancer 61: 337, 1990.

10. Darby, S.C. and Pike, M.C., "Response to the Letter from Dr. Wald," British Journal of Cancer 61: 337-338, 1990.

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A QUANTITATIVE ESTIMATE OF NONSMOKERS' LUNG CANCER RISK FROM PASSIVE SMOKING

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This work presents a quantitative assessment of nonsmokers' risk of lung cancer from passive smoking. The estimates given should be viewed as preliminary and subject to change as improved research becomes available. It is estimated that U.S. nonsmokers are exposed to from 0 to 14 mg of tobacco tar per day, and that the typical nonsmoker is exposed to 1.4 mg per day. A phenomenological exposure-response relationship is derived, yielding 5 lung cancer deaths per year per 100,000 persons exposed, per mg daily tar exposure. This relationship yields lung cancer mortality rates and mortality ratios for a U.S. cohort which are consistent to within 5% with the results of both of the large prospective epidemiological studies of passive smoking and lung cancer in the United States and Japan. Aggregate exposure to ambient tobacco smoke is estimated to produce about 5000 lung cancer deaths per year in U.S. nonsmokers aged ≥ 35 yr, with an average loss of life expectancy of 17 ± 9 yr per fatality. The estimated risk to the most-exposed passive smokers appears to be comparable to that from pipe and cigar smoking. Mortality from passive smoking is estimated to be about two orders of magnitude higher than that estimated for carcinogens currently regulated as hazardous air pollutants under the federal Clean Air Act.

Introduction

Exposure of nonsmokers to indoor air pollution from tobacco smoke (also known as involuntary or passive smoking) has recently become a public health concern (USSG, 1982) for several reasons: such exposure is widespread (Repace and Lowrey, 1980; Friedman *et al.*, 1983); studies of the effects of tobacco smoke on smokers worldwide have implicated it as the most important cause of lung cancer (USSG, 1982; Doll and Peto, 1981); existence of a threshold for carcinogenesis is doubtful (USSG 1982; IRLG, 1979; U.S. EPA, 1979a; IARC, 1979; Pitot, 1981); and there is suggestive new evidence of lung cancer (and other serious health effects) in nonsmokers exposed to ambient concentrations of tobacco smoke (Trichopoulos, 1981, 1983; Hirayama, 1981a, 1981b, 1983a, 1983b; Garfinkel, 1981; Correa *et al.*, 1983; Knoth *et al.*, 1983; Gillis *et al.*, 1983; Koo *et al.*, 1983; Kabat and Wynder, 1984; Miller, 1984; Sandler *et al.*, in press a,b).

There are three important fractions of tobacco smoke: mainstream smoke, which the smoker inhales directly into the lung; exhaled mainstream smoke, that fraction of the mainstream smoke which is not retained in the lungs of the smoker, and sidestream smoke, that fraction of tobacco smoke emanating directly from the burning end of the cigarette into the air. Nonsmokers are commonly exposed to tobacco combustion products in diluted sidestream and exhaled mainstream tobacco smoke from cigarettes, cigars, and pipes (Repace and Lowrey, 1980). Tobacco smoke contains 60 known or suspect carcinogens, including 51 in the phase containing particulate matter; the carcinogenic activity of tobacco smoke appears to require this phase (USSG, 1982). Animal bioassays indicate that sidestream tobacco tar is more carcinogenic per unit weight than mainstream tar (Wynder and Hoffman, 1967). For public health purposes, it will be assumed that mainstream and sidestream smoke have similar human carcinogenic potency.

In his 1982 report on cancer and smoking (USSG, 1982), the U.S. Surgeon General asserted that despite the incompleteness of the evidence, nonsmokers should

*The views presented in this article are those of the authors, and do not necessarily reflect the policies of their respective agencies.

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avoid exposure to second-hand smoke to the extent possible, a risk-management judgement supported by the World Health Organization and the National Academy of Sciences (WHO, 1979; NRC, 1981).

This raises the question of whether the quantity of tobacco tar to which the average nonsmoker is exposed creates a significant risk of lung cancer. In order to answer this question, a quantitative risk assessment is first justified and then performed. Risk assessment is the use of science to define the health effects of exposure of individuals or populations to hazardous materials or situations (NRC, 1983). Risk assessments contain some or all of the following four steps:

(1) Hazard identification—the determination of whether a particular chemical is or is not causally linked to certain health effects.

(2) Dose-response assessment—the determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.

(3) Exposure assessment—the determination of the extent of human exposure before or after application of regulatory controls.

(4) Risk characterization—the description of the nature and often the magnitude of the human risk, including attendant uncertainty.

In other words, quantitative risk assessment deals with the question of how much morbidity and mortality an agent is likely to produce given specified levels of exposure. Typically utilized in the regulation of carcinogens, it is important because control efforts cannot proceed without assurance that the health gains are worth the cost (Lave, 1983; Albert, 1983). On the basis of such assessments, informed risk management judgements can be made.

This work draws upon the epidemiology of lung cancer (USSG, 1982; Pitot, 1981; USSG, 1979; Ives, 1983) and on indoor air pollution physics (Repace and Lowrey, 1980, 1982; NRC, 1981) to produce a risk analysis (IRLG, 1979; U.S. EPA, 1979a; Lave, 1983; COST, 1983; Fischoff *et al.*, 1981; NRC, 1983) in which nonsmokers' lifestyles are correlated to exposure to airborne tobacco tar, and incidence of lung cancer. This analysis first reviews estimates of the average exposure of the general population of ambient tobacco smoke. Second, it reviews studies linking tobacco-related disease in nonsmokers to exposure-related variations in lifestyle. Third, it couples these two factors to develop a phenomenological estimate for the aggregate lung cancer risk to the U.S. nonsmoking population, and develops an exposure-response relationship for the estimation of the risk to the most-exposed. Fourth, it compares the estimated level of lung cancer mortality and resultant loss of life expectancy from passive smoking to those from cigarette, pipe, and cigar smoking. Fifth, it compares the predictions of alternate exposure-response relationships with the results of two large prospective epidemiologic studies of passive smoking and lung cancer, and performs a sensitivity analysis. Finally this work compares the estimated risk from ambient tobacco smoke to that from various airborne carcinogens currently being regulated in the United States as hazardous air pollutants, to place the significance of the estimated risk in perspective.

Variation of Exposure with Lifestyle

In earlier work (Repace and Lowrey, 1980, 1982, 1983, 1984; Repace, 1981, 1982, 1983, 1984, in press; Repace *et al.*, 1980, 1984; Bock *et al.*, 1982) factors affecting nonsmokers' exposures to tobacco smoke were studied, and field surveys of the levels of respirable particles were conducted indoors and out, in both smoke-free and smoky environments. This work established that ambient tobacco smoke imposed significant air pollution burdens on nonsmokers, and, using controlled experiments (Repace and Lowrey, 1980, 1982, 1983), a model was developed to estimate those exposures. This model predicts that the exposure of U.S. nonsmokers ranges from 0 to 14 mg of cigarette tar per day (mg/d), depending upon the nonsmokers's lifestyle. As derived in Appendix A and shown in Table 1, the average population exposure for adults of working age, averaging over the work and home microenvironments, is about 1.43 mg/day (Repace and Lowrey, 1983) with an 86% exposure probability.

Table 1, derived from the model in Appendix A, estimates probability-weighted exposure to the particulate phase of ambient tobacco smoke for a typical U.S. adult nonsmoker. Exposures received in other (Repace *et al.*, 1980) indoor microenvironments, outdoors, and in transit, which account for the remaining 12% of people's time, were omitted. Table 1 is derived from considerations that ambient concentrations of tobacco tar have been found to be directly proportional to the smoker density and inversely proportional to the ventilation rate (Repace and Lowrey, 1980). Ventilation rate tables given by ASHRAE (1981), can be used to estimate both the range in ventilation rate (from the design mechanical rates) and smoker density (from the design occupancies), and thus upper and lower bounds and average concentrations for model workplace and home microenvironments can be estimated.

Table 1 suggests that individuals receiving exposure both at home and at work constitute a high exposure group, with the workplace appearing four times as strong a source of exposure as the home; the reason for this differential is the generally higher occupancy (i.e., smoker density) encountered in the workplace (Repace and Lowrey, 1982; ASHRAE, 1981). This estimate of exposures represents a modeled weighted average taken over the entire population, including those who are not exposed.

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Table 1. Estimated probabilities of nonsmokers' exposure to tobacco smoke at home and at work (after Repace and Lowrey, 1983; Appendix A).[a] Nonexclusive probability of being exposed at work: 63%; probability of *not* being exposed at work: 37%. Nonexclusive probability of being exposed at home: 62%; probability of *not* being exposed at home: 38%.

Lifestyle: Daily Average Probability of Being Exposed (Rounded Values)		Exposure (mg) Modeled Daily Average	Daily Probability-Weighted
At work and at home: %	63 × 62 = 39	2.27	0.89
Neither at work nor at home: %	37 × 38 = 14	0.00	0.00
At home but not at work: %	62 × 37 = 23	0.45	0.10
At work but not at home: %	63 × 38 = 24	1.82	0.44
Total: %	100		1.43

[a]The estimated exposure to the particulate phase of ambient tobacco smoke for U.S. adults of working age, at work and at home (these two microenvironments account for an estimated 88% of the average person's—both smokers and nonsmokers—time), determined from average concentrations of tobacco smoke calculated for model workplace and home microenvironments, weighted for average occupancy, as derived in Appendix A.

Jarvis and Russell (in press), in a study of urinary cotinine (a nicotine metabolite) in a sample of 121 self-reported nonsmokers, state that only 12% of subjects had undetectable cotinine levels, despite nearly 50% reporting no passive smoke exposure. In a study of 472 nonsmokers, Matsukura (1984) examined the relationship of urinary cotinine to the smokiness of their environment, and found that nonsmokers who lived or worked with smokers had higher cotinine levels than those who did not. Matsukura *et al.*, (1984) also found that cotinine levels increased with the number of smokers present in the home and the workplace; however, none of the differences were statistically significant, except for the lowest urinary cotinine level of the nonsmokers who were not exposed to tobacco smoke in the home or the workplace. These studies respectively illustrate the widespread exposure of nonsmokers to ambient tobacco smoke, and the relative importance of the domestic and workplace microenvironments in such exposures.

Epidemiological Evidence for the Variation of Risk with Lifestyle: Pulmonary Effects

White and Froeb (1980) evaluated the effect of various degrees of long-term (>20 yr) workplace exposure to tobacco smoke on 2100 healthy middle-aged workers. Of these workers, 83% held professional, managerial, or technical positions, while the remaining 17% were blue-collar workers. Relative to those not exposed at home or at work, passive smokers of both sexes suffered statistically significant declines in mid- and end-expiratory flow rates which averaged about 13.5% and 22% respectively, and did not differ significantly from the values measured in nonsmoking or light smokers of cigarettes, pipes, and cigars. They concluded that chronic exposure to tobacco smoke in the work environment reduces small airways function to the same extent as smoking 1 to 10 cigarettes per day.

Kauffmann *et al.* (1983) compared pulmonary function in about 3800 people in France: 849 male "true" nonsmokers (defined as those not exposed at home), 165 male passive smokers (defined as those exposed at home), 826 female "true" nonsmokers, and 1941 female passive smokers. The authors restricted the analysis to subjects aged 40 yr or older (i.e., to those who had been exposed for 15 or more years to smoking by their spouses) and who were living in households with no persons over the age of 18 yr except their spouses. They found that nonsmoking subjects of either sex whose spouses were current smokers of at least 10 g (about 10 cigarettes) of tobacco a day had mid-expiratory flow rates averaging 11.5% lower than those married to nonsmokers. For women in social classes with the highest percentage of paid work, the effect of workplace smoking appeared to confound the effect of passive smoking at home. However, in the large subgroup of women without paid work (i.e., not exposed to workplace smoking), a clear dose-response relationship to amount of husbands' smoking was observed. They concluded that women living with heavy smokers appeared to have the same reductions in mid-expiratory flow rates as light smokers, and that after 15 yr exposure in the home environment, passive smoking reduces pulmonary function.

A third study by Kasuga (1983) of urinary hydroxyproline-to-creatinine (HOP-r) ratios as a function of passive smoking status showed that HOP-r levels in nonsmoking wives and children varied in a dose-response relationship with husbands' and parental smoking habits, when adjusted for pre-existing respiratory disease. Kasuga (1983) asserts that HOP-r serves as a marker to detect deleterious active and passive smoking effects on the lung, before and after the manifestation of clinical symptoms, and that urinary HOP-r in light-smoking women is almost equivalent to HOP-r in nonsmoking wives with heavy-smoking husbands.

These three epidemiologic studies provide evidence that variations in the exposure of adult nonsmokers to ambient tobacco smoke at home and, particularly, at

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work, can produce observable pulmonary effects. Like effects have been observed in children exposed at home (Tager *et al.*, 1983).

Cancer

Thirteen epidemiologic studies have explicitly examined the lung cancer risk incurred by the nonsmoking spouses of cigarette smokers. In all but one study, the only exposure variable was the strength of the spouse's smoking habit. The studies were conducted in Greece (Trichopoulos *et al.*, 1981, 1983), Japan (Hirayama, 1981a, 1981b, 1983a, 1983b), the United States (Garfinkel, 1981; Correa, *et al.*, 1983; Kabat and Wynder, 1984; Miller, 1984; Sandler, *et al.*, a and b, in press), Germany (Knoth *et al.*, 1983), Scotland (Gillis *et al.*, 1983), and Hong Kong (Chan and Fung, 1982; Koo *et al.*, 1983).

In the Greek study, Trichopoulos *et al.* (1981, 1983) used the case-control technique: involuntary exposure to cigarette smoke as measured by the husbands' daily consumption was found to increase the average risk of lung cancer by a factor of 2.4 ($p < 0.01$) when 77 lung cancer patients were compared to 225 controls, and a dose-response relationship was observed. Divorce, remarriage, husband's death, and change in smoking habits were considered.

In the Japanese study (from 1966 to 1981) of lung cancer in 91,540 nonsmoking women, Hirayama (1981a, 1981b, 1983a, 1983b) used the prospective technique: relative to those women not exposed at home (controls), involuntary exposure of wives of smokers was found to increase the average risk of lung cancer by a factor of 1.78 ($p < 0.001$), where the exposure was also estimated from husbands' daily consumption. The annual lung cancer death (LCD) rate in the controls was 8.7 per 100,000. Hirayama found that the exposed wives experienced an average annual increase in lung cancer mortality rate of 6.8 per 100,000, with a range of 5.3 to 9.4 per 100,000, in a dose-response relationship depending upon the degree of the husband's smoking. Hirayama found further that the risk of lung cancer death in nonsmoking women increased both with the time of exposure and number of cigarettes smoked daily by the husband. Hirayama also reported a factor of 2.9 (± 0.3, at the 95% confidence level) for increased risk of lung cancer in 1010 nonsmoking husbands with smoking wives.

More recently, Hirayama extended his earlier work to suggest increased risk of nasal sinus cancer, and ischemic heart disease in passive smokers, and evidence of decreased lung cancer risk in nonsmoking wives of exsmokers. With respect to cancer of the para-nasal sinuses in nonsmoking wives ($n = 28$), Hirayama found standardized mortality ratios of 1.00, 2.27, 2.56, and 3.44 when husbands were nonsmokers, smokers of 1–14, 15–19, and >20 cigarettes per day, respectively ($p = 0.01$). For ischemic heart disease, risk elevations for nonsmoking wives ($n = 494$) with the extent of husbands' smoking were reported, with standardized mortality ratios of 1.00, 1.10, and 1.31 when husbands were nonsmokers, smokers of 1–19, and >20 cigarettes/day, respectively ($p < 0.02$). For lung cancer, the standardized mortality ratio of lung cancer in nonsmoking women ($n = 200$) was 1.00, 1.36, 1.42, 1.58, and 1.91 when husbands were nonsmokers, exsmokers, daily smokers of 1–14, 15–19, and >20 cigarettes/day, respectively.

In the first U.S. study, Garfinkel (1981) reported results from an analysis of data collected from the American Cancer Society's (ACS) prospective study of lung cancer risk in 176,739 nonsmoking white women (1960 to 1972) as a function of involuntary exposure as indicated by their husbands' cigarette consumption. Of the total, 72% of the nonsmoking women were married to smokers. Three smoking categories were identified: none, less than one pack (20 cigarettes) per day, or greater than one pack per day. Garfinkel reported statistically insignificant risk ratios of 1.00, 1.27, and 1.10, respectively, for the three categories (average 1.20 over the exposed categories). Also reported were age-standardized death rates, which were respectively 13.8, 12.9, and 13.1 lung cancer deaths per 100,000 person-yr for this cohort in 1960–1964, 1964–1968, and 1968–1972 (average 13.3 per 100,000 person-yr for the period 1960–1972). The death rates were standardized to the distribution of white men and women combined for the U.S. population in 1965, which decreased the rates for females "slightly."

More recently, Correa *et al.* (1983) studied 8 male and 22 female nonsmoking lung cancer cases and 180 male and 133 female controls as part of a larger study including smokers, with 1338 lung cancer cases and 1393 controls, in Louisiana. They reported that nonsmokers married to heavy smokers had an increased risk of lung cancer, as did smokers whose mothers smoked. Men with smoking wives had a nonsignificant risk ratio of 2.0 compared to their counterparts with nonsmoking wives, and women with smoking husbands had an average risk ratio of 2.07 ($p < 0.05$) compared to women with nonsmoking husbands. An exposure-response relationship was observed, with the peak risk reaching 3.5 ($p < 0.05$). The combined data for men and women passive smokers was significant ($p < 0.05$) for the heavier smoking category (≥ 41 pack-years).

A third U.S. case-control study, by Kabat and Wynder (1984), reported on passive smoking and lung cancer in nonsmokers for 25 male cases and 25 controls, and 53 female cases and 53 controls, where the majority of the patients were from New York City. The controls consisted of patients hospitalized for non-smoking-related diseases, roughly two-thirds being cancer patients. No differences on exposure to passive smoking at home or at work were found in the women. However,

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the male passive smokers displayed a statistically significant ($p = 0.05$) difference in lung cancer (odds ratio 1.6) relative to the non-exposed group.

A fourth U.S. study by Miller (1984) of mortality from all forms of cancer in 123 nonsmoking women (only 5 lung cancer cases) as a function of husband's smoking history reported a nonsignificant odds ratio of 1.4 for all women ($p = 0.15$) for women whose husbands smoked relative to those who did not; when employed women were excluded, the odds ratio increased to 1.94 and was statistically significant ($p < 0.02$).

A fifth U.S. study of Sandler *et al.* (in press a) also examined mortality from all forms of cancer related to passive smoking, in both nonsmokers and smokers [231 cases and 235 controls (70% white and 67% female); only 2 cases of lung cancer in nonsmokers] as a function of spouses' smoking habits. Cancer risk—adjusted odds ratio—(lung, breast, cervix, and endocrine) among individuals ever married to smokers was 2.0 times that among those never married to smokers ($p < 0.01$). This increased risk was not explained by confounding individual smoking habits, demographic characteristics, or social class.

In a sixth U.S. study, Sandler *et al.* (in press b) examined cancer risk in adulthood in 197 cases and 223 controls, 66% female, from early life exposure to parents' smoking. They found that mothers' and fathers' smoking were both associated with risk for hematopoietic cancers (Hodgkin's disease, lymphomas, and leukemias), and a dose-response relationship was seen for the latter two. The odds ratio for hematopoietic cancers increased from 1.7 when one parent smoked, to 4.6 when both smoked ($p < 0.001$).

In the first of two studies from Hong Kong, Chan and Fung (1982) found a lower incidence of passive smoking among 34 female lung cancer cases (40.5%) than among 66 female controls (47.5%). All patients and controls were interviewed concerning their smoking habits and those of their spouses, their cooking habits, including types of cooking fuel used. Histological diagnoses of tumors were obtained. Controls were taken from orthopedic patients.

In the second Hong Kong study, Koo *et al.* (1983) studied passive smoking in 56 female lung cancer cases and 85 female controls. Passive smoking cases had an excess of 3.8 yr of passive smoking (workplace plus domestic exposures) compared with controls, but the differences were not statistically significant ($p \leq 0.069$). However, among a subgroup of 8 marine dwellers, cases had 11.8 years more exposure than controls ($p = 0.0003$).

Knoth *et al.* (1983) reported on a study of 39 nonsmoking German females with lung cancer. 61.5% were found to have smoking spouses. The authors state that this percentage was threefold that expected on the basis of smoking habits of German males.

Gillis *et al.* (1984) reported preliminary results of a study of passive smoking and lung cancer in 91 male controls ($n = 2$) [the numbers in parentheses give the numbers of cases] without domestic passive smoking and in 90 subjects exposed at home ($n = 4$), and in 40 female controls ($n = 2$) and 58 subjects ($n = 6$). No effects of lung cancer were noted in the females, but elevated rates of myocardial infarction were reported (risk ratio 3.0). In the males, elevated rates of both lung cancer (risk ratio 3.25) and myocardial infarction (risk ratio 1.45) were reported. Gillis *et al.* state that since insufficient time has elapsed since the beginning of this study, no firm conclusions can be drawn relating to the incidence of cancer or other diseases.

Thus there are now a large number of studies providing evidence for increased risk of lung cancer from increased exposure to passive smoking. It might be expected that subgroups of the population which proscribe smoking among their membership would have a lower probability of passive smoking, and therefore should also have a lower incidence of smoking-related disease than the general nonsmoking population.

One such subgroup is the Church of Jesus Christ of the Latter Day Saints, popularly known as the Mormon Church, which advises against the use of tobacco. Enstrom (1978) found that active Mormons who were nonsmokers had standardized mortality rates for lung cancer which were 21% of those in the general population which includes smokers. This rate was found comparable to the rate of 19% for a sample of the U.S. general population "who had never smoked cigarettes." Interestingly, however, this result occurred despite the fact that 31% of the active Mormon cohort were former smokers. This confounding factor was not present for certain subgroups in the following study.

Phillips *et al.* (1980a, 1980b) have studied mortality (from 1960 to 1976) in Seventh Day Adventists (SDAs), a religious group that also follows rigorous proscriptions against the use of tobacco. As with the Mormons, SDAs have rates of mortality from lung cancer and other smoking related cancers that are fractions, 21% and 66%, respectively, of the rates for a demographically comparable group in the general U.S. population (including smokers) (1980a). Many SDAs work for church-run businesses. Thus, SDAs appear to be less likely than the general population to be involuntarily exposed to tobacco smoke, as children or as adults, at home or in the workplace, because neither SDA homes nor SDA businesses are likely to be places where smoking is permitted, and because the great majority of SDA family and social contacts are among other SDAs who do not smoke (See Appendix C).

Phillips *et al.* (1980a, 1980b) compared mortality in two demographically similar groups of Southern Californians: SDAs (from 1960 to 1976) and non-SDAs (from 1960 to 1971). A sizable subgroup (35%) of SDAs report prior cigarette use, especially among men (1980b). However, for two select subgroups of each group, 25,264 SDAs and 50,216 non-SDAs who were self-reported

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Table 2. Age-adjusted SDA-to-non-SDA ratio of lung cancer mortality (after Phillips *et al.* (1980b).[a]

	Average	By Health Habit Index: Best Third	Average Third	Worst Third
I. All SDAs	0.54	0.54	0.40	0.96
II. SDAs who never smoked	0.41	0.41	0.32	0.78

Values shown are adjusted by Mantel-Haenzel procedure ($p \leq 0.01$).

[a]Lung cancer mortality ratios taken from a prospective study of two demographically similar cohorts. The non-SDA come from the general south California population, and were self-reported nonsmokers who never smoked. The SDA come from a southern California subgroup less likely to engage in passive smoking by virtue of lifestyle differences. The health habit index is a measure of how faithfully individuals adhered to the Church's teachings; the worst third were also more likely to have a non-SDA spouse. (Values quoted in text are the reciprocals of numbers given here.) Phillips *et al.* (1980a, 1980b) reported results for all SDA, and reported replicating these data for SDA who never smoked, as shown. The SDA subjects and non-SDA subjects for this study consisted of white California respondents to the same four-page self-administered questionnaire collected by the American Cancer Society study of 1 million subjects throughout the United States (NCI, 1966; Garfinkel, 1981; Phillips *et al.*, 1980a, 1980b).

nonsmokers who had never smoked, age-adjusted mortality rates were compared for smoking-related and nonsmoking-related diseases. Table 2 compares age-adjusted lung cancer mortality ratios for two SDA cohorts relative to nonsmokers in the general population who never smoked. The first cohort consists of all SDA, and includes those who never smoked, exsmokers, and smokers. The first row of Table 2 gives the mortality ratios relative to the never-smoked non-SDAs in the general population. The second row compares the second SDA cohort (those who never smoked) to the non-SDA who never smoked. The values given are averaged over both sexes. From Table 2 the results show that the non-SDA group of nonsmokers who had never smoked (but who were more likely to suffer involuntary exposure to tobacco smoke) had an average lung cancer mortality rate of 2.4 times that of the never-smoked SDAs (the group less likely to have suffered such exposure by virtue of their lifestyle). This concludes the review of evidence relating variations of lifestyle to variations in lung cancer risk in nonsmokers.

Does Ambient Tobacco Smoke Pose a Carcinogenic Hazard?

The International Agency For Research on Cancer (IARC) criteria for causality to be inferred between exposure and human cancer state that confidence in causality increases when (1) independent studies agree; (2) associations are strong; (3) dose-response relationships exist, and (4) reduction in exposure is followed by reduction in cancer incidence (IARC, 1979). These criteria are applied here as follows:

1. There are now 14 studies, covering 6 cultures, indicating a relationship between exposure to ambient tobacco smoke and incidence of lung cancer. If the studies are divided into substudies of men and women, this yields 20 substudies, all but 2 of which suggested an increased cancer mortality from passive smoking, and 12 of which attained statistical significance. Moreover, the mortality ratios based on spouses' smoking as an exposure variable, cluster around the value 2.0. Thus, many independent studies agree.

2. Mainstream tobacco smoke is strongly associated with lung cancer. The U.S. Surgeon General (USSG, 1982) asserts that mainstream cigarette smoke is a major cause of cancers of the lung, larynx, oral cavity, and esophagus, and is a contributory factor for the development of cancers of the bladder, pancreas, and kidney, where the term contributory factor does not exclude the possibility of causality. Both smokers and nonsmokers are exposed to exhaled mainstream and sidestream tobacco smoke. Sidestream smoke by animal bioassay has been found to be of greater potency than mainstream smoke.

3. Five of the 14 studies reported dose-reponse relationships between passive smoking and lung cancer. Dose-response relationships between lung cancer and active cigarette smoking show increasing mortality with increasing dosage of smoke exposure, and an inverse relationship to age of initiation (USSG, 1982). Dose-response relationships are also shown for smokers whose smoking habits are like heavy passive smoking (Wynder and Goodman, 1983; Jarvis and Russell, in press), i.e., in cigarette smokers who do not inhale, and in pipe and cigar smokers, who also are unlikely to inhale (USSG, 1982; USSG, 1979).

4. Reductions in lung cancer incidence for reduction in exposure have been found in all major studies of active smoking (USSG, 1982). The one study of passive smoking and lung cancer which examined this question also found a similar result (Hirayama, 1983b). Furthermore, the comparison of the SDAs who never smoked, and who should have reduced exposure relative to the non-SDAs who never smoked, also appears to exhibit this effect.

On the basis of the IARC criteria, the evidence appears to be sufficient for reasonable anticipation of an increase in lung cancer mortality from passive smoking, justifying a quantitative risk assessment. The significance of the public health risk will now be estimated.

Estimation of Total LCD Risk and a Phenomenological Exposure-Response Relationship

A phenomenological exposure-response relationship is now derived based on consistency (Hirayama, 1983b)

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of evidence provided by studies of lung cancer in nonsmokers and from our exposure assessment. The Seventh Day Adventist Study by Phillips *et al.* (1980a, 1980b) appears to provide the best evidence of the magnitude of the lung cancer effect from passive smoking among U.S. nonsmokers.

A calculation (Appendix C) based on the age-standardized differences in lung cancer mortality rates between SDAs who never smoked and demographically comparable non-SDAs who never smoked (age groups 35 to 85+) from the studies of Phillips *et al.* (1980a, 1980b) yields an estimated 4700 lung cancer deaths (LCDs) for the 62.4 million U.S. nonsmokers (USDC, 1980) at risk (USSG, 1979) aged ≥ 35 yr. This in turn yields a passive smoking risk rate of 7.4 LCDs per 100,000 person-yr (4700 LCDs/yr per 62,424,000 persons), in good agreement with the value of 6.8 per 100,000 person-yr reported in the Hirayama (1981) study. To place the estimated mortality in perspective, 4700 deaths was about 5% of the total annual LCDs, and about 30% of the LCDs in nonsmokers in 1982 (USSG, 1982).

The exposure of nonsmokers in the U.S. population of working age, taken from the model results in Table 1, appears to be a weighted average of about 1.43 mg of tobacco tar per day, including the estimated 14% of the population who received no exposure at home or work. The carcinogenic risks will be assumed to apply even to retired persons, whose exposures are reported to be less than the employed (Friedman *et al.*, 1983), because the risks of lung cancer from smoking decline only slowly even with total cessation of exposure (USSG, 1982), and because the risks of lung cancer increase exponentially with age (NCI, 1966).

Using the statistical risk of 7.4 LCDs per 100,000, and dividing by the average exposure of 1.43 mg/day, we estimate a phenomenological exposure-response relation appropriate for the general U.S. population at risk, of about 5 LCDs per 100,000 person-yr at risk per 1 mg/day nominal exposure.

The range in nominal exposure has been estimated to be 0–14 mg/day (Repace and Lowrey, 1980). Studies of lung cancer and passive smoking across three cultures have shown an exposure-response relationship. Thus, the assumption of an exposure-response relationship is justified, and a linear exposure-response function (Doll and Peto, 1981; IRLG, 1979; U.S. EPA, 1979; Crump *et al.*, 1976) is assumed. With zero excess risk from tobacco smoke for zero exposure, and applying the exposure-response relationship derived above, with the maximum exposure of 14 mg/day, a maximum risk of about (14 × 5) = 70 LCDs per 100,000 person-yr is estimated for the most-exposed lifestyle. This lifestyle has been previously typified by that of a nonsmoking musician who performs regularly in a smoky nightclub and who resides in a small apartment with a chainsmoker; many other scenarios may be drawn (Repace and Lowrey, 1980).

Estimated Loss of Life Expectancy

Reif (1981a, 1981b) argues that there exists a genetically determined distribution in natural susceptibility to lung cancer in people; the effect of exposure to tobacco smoke is to shift this distribution toward death at earlier ages. In other words, exposure to tobacco smoke produces a loss of life expectancy. One method of presenting risk data involves calculation of the loss of life expectancy, in units of days of life lost per individual, averaged over the entire population at risk. When the average life-loss is multiplied by the number of individuals at risk, the impact of the hazard on society in person-yr of life lost can be assessed. More important, one can display the age-specific probabilities of death from the hazard, as well as the average number of years of life lost by the average victim. Appendix C gives the method of calculation.

Averaged over all of the population at risk, (i.e., including those who die of other causes), the average loss of life expectancy from passive smoking is calculated (appendix C) to be 15 days, which is equivalent to an ultimate loss of 2.5 million person-yr of life for the total at-risk U.S. population in 1979 over 35 yr of age (62.4 million persons). The estimated worst-case loss of life expectancy is 148 days, again averaged over all of the population at risk. The estimated mean life expectancy lost by a passive-smoking lung cancer *victim* is 17 ± 9 yr.

How does the calculated average loss of life expectancy for heavy passive smoking compare with the average loss of life expectancy found in active smokers? The modeled worst-case lifestyle might be reasonably expected to have lesser exposure, and hence lesser risk than active smokers. Table 3, adapted from Cohen and Lee (1979), gives this comparison. The estimated most-exposed lifestyle has about ⅔ the loss of life expectancy of the average pipe smoker, about ½ the loss of the

Table 3. Estimated loss of life expectancy from active smoking (all causes) and passive smoking (lung cancer only), adapted from Cohen and Lee (1979).

Cause	Days
Cigarette smoking – male	2250
Cigarette smoking – female	800
Cigar smoking	330
Pipe smoking	220
Passive Smoking[a] (est. most exposed lifestyle)	148
Passive smoking[a] (est. average lifestyle)	15

[a]Estimated this work (see Appendix C); averaged over all nonsmokers at risk, i.e., those who are presumed to die from passive smoking-induced lung cancer, and those who do not. Estimates given for passive smoking are phenomenological estimates.

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average cigar smoker, and 1/10 of that for active cigarette smoking.

Estimate of an Exposure-Response Relationship Based on Risks in Smokers

An alternative extrapolated exposure-response relationship is now derived from evidence provided by studies of lung cancer in cigarette smokers. Using the Surgeon General's estimate that 85% of all lung cancers are due to smoking (USSG, 1982), a current annual LCD rate to smokers at risk of about 316 per 100,000 is estimated (see Appendix B). Assuming a one-hit model (see Appendix B) for extrapolation of the risk (which in this range is functionally equivalent to the linear assumption that a milligram of tobacco tar inhaled by a nonsmoker produces a response equivalent to that in a smoker) yields an estimate of about 0.87 LCDs/100,000 person-yr. This corresponds to an exposure-response relationship of 0.6 LCDs/ 100,000 person-yr per mg/day, and an annual aggregate risk estimate of about 555 LCDs per year, an order of magnitude lower than the phenomenological estimate.

Discussion of Alternative Exposure-Response Relationships

We now speculate on why these two different methods produce such disparate estimates of risk. One possibility is that nonsmokers may have a reduced tolerance to the effects of tobacco smoke. Another possibility is a "large dose" effect (Jarvis and Russell, in press), whereby exposure to tobacco tar at the lesser doses experienced by nonsmokers produces a greater risk per unit dose than the greater doses experienced by active smokers, whose lung tissue is saturated by carcinogenic tar. Large dose effects have been observed in cancer induction by ionizing radiation, in which the dose-response curve has a linear form at low doses, a quadratic upward (positive) curvature at intermediate doses, but a downward (negative) curvature at high doses (NRC, 1980). Downturns in exposure-response curves of lung cancer in smokers of more than 40 cigarettes per day have been observed by Doll and Peto (1978) and Hirayama (1974). The effect of a leveling-off or downturn in the exposure-response curve at large exposures would be to cause a linear model to underestimate the risk when extrapolated (Hoel *et al.*, 1975, 1983; NRC, 1980) over two orders of magnitude to low exposures.

A third possibility is generated by modeling the dose, as opposed to the exposure, of nonsmokers to tobacco smoke. Nonsmokers' exposure is translated into dose by means of a simple single-compartment model for lung deposition and clearance (Repace, 1983). This model suggests that tar may accumulate on the surface of nonsmokers' lungs to an equilibrium dose an order of magnitude higher than the nominal exposure, to a level of about 16 mg/day, due to the long pulmonary residence times for respirable aerosols. If this 16-mg dose, rather than the 1.4-mg exposure, is the operative factor, then the typical passive smoker would have a risk, according to the one-hit model, of about 9 per 100,000, in agreement with the phenomenological estimate.

There is support for this argument from Matsukura's study (1984), which showed that heavy passive smokers had urinary cotinine levels comparable to active smokers of less than 3 cigarettes per day, and from Kasuga's study (1983), which also showed that heavy passive smokers had urinary hydroxyproline levels almost equivalent to that of light smokers. Moreover, similar observations have been found indicating that serum thiocyanate (Cohen and Bartsch, 1980) and benzpyrene (Repetto and Martinez, 1974) levels in some passive smokers were comparable to the elevated levels typically found in smokers.

The simple model we have proposed ignores the effect of cancer latency. The long latency period for lung cancer indicates that childhood passive smoking may be an important factor affecting risk in adult life: Doll and Peto (1981) have suggested that the effect of passive smoking may be surprisingly large because lifelong exposure may produce a lung-cancer effect four times as great as that which is limited to adult life (recall the observation of Sandler *et al.*, in press: childhood passive smoking appeared to elevate the cancer risk of adults). As Bonham and Wilson (1981) have shown from a national study of 40,000 children in 1970, 62% came from homes with one or more smokers, indicating that many adults receive exposure during childhood.

Sensitivity Analysis

Which of the two exposure-response relationships derived is more useful in explaining actual epidemiological data? The Garfinkel (1981) American Cancer Society (ACS) study of passive smoking and lung cancer, which spanned the years 1960 to 1972, reported a standardized mortality ratio of 1.20 and an annual lung cancer rate of 13.3 per 100,000 person-yr. Of the 176,739 women in the Garfinkel study, 28% had nonsmoking husbands. Thus, the "controls" numbered 49,487 and the total "exposed" were 127,252. According to census data (U.S. Dept. of Commerce, 1980), female participation rates in the labor force ranged from 37.1% in 1960 to 38.8% in 1965, 42.8% in 1970, and 43.7% in 1975, and were about 80% of the 1965 level in 1947. Thus, it appears that about 38% of the women in this study were in the labor force, and presumably exposed to passive smoking while at work. It is assumed that for both groups of women, control and exposed, 38% were employed and exposed to ambient tobacco smoke while at work.

As indicated in Table 1, typical U.S. nonsmoking

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Group	Number
Total cohort	176,739
"True" controls; do not work, husbands do not smoke	30,682
"Tainted" controls: work, husbands do not smoke	18,805
Total "controls"	49,487
"Exposed" workers: work, husbands smoke	48,356
"Exposed" nonworkers: do not work, husbands smoke	78,896
Total "exposed"	127,252

adults are estimated to inhale 1.82 mg of tobacco tar per average day at work and 0.45 mg per average day at home, an exposure ratio of 4:1. This occurs because, although domestic and workplace air exchange rates are similar (Appendix A), workplace smoker densities tend to be far higher. Let the assumed basal rate of lung cancer deaths in these women from causes other than passive smoking be 8.7 per 100,000 (the age-adjusted rate for nonsmoking women married to nonsmokers in Hirayama's study, 1981a). The Garfinkel (1981) ACS cohort can now be broken down as shown in Table 4.

The Garfinkel (1981) study can be analyzed as follows, using the phenomenological exposure-response relationship of 5 LCDs/100,000 person-yr-mg/day.

The lung cancer deaths per 100,000 contributed by passive smoking are then 2.25 (0.45 × 5) for the home and 9.10 (1.82 × 5) for the workplace. Application of these figures to the numbers of true and tainted controls and working and nonworking exposed women yields, after addition of the basal risk of 8.7 per 100,000, the estimated rates for lung cancer deaths per 100,000 person-yr, as shown in Table 5. The ratio of risks (all exposed:all controls) is thus 1.19. The ratio (averaged over husbands' heavy and light smoking categories) in the Garfinkel (1981) study was 1.20, less than a 1% difference. The lung cancer death rate for the weighted average of the "exposed" and "control" categories is 13.8 per 100,000. Over the 12 yr of the Garfinkel study, the actual rate averaged 13.3 per 100,000, a less than 4% difference. In other words, this analysis (Repace, 1984) appears to explain both the observed lung cancer death rate and observed risk-ratio of the Garfinkel ACS cohort.

Could this be due to chance? Suppose that, instead of 38% of women in the workforce, 100% of women lung cancer death rate would be 19.42, a 46% difference. Suppose 0% of women worked. Then the ratio of risks would be 1.26, a 5% difference from Garfinkel's result, but the lung cancer death rate would be 10.32 per 100,000, a 22% difference from Garfinkel's observation.

Suppose the exposure-response relationship of 0.6 LCDs/100,000 person-yr per mg/day yielded by extrapolation with the one-hit model from the risks in smokers is used. The lung cancer deaths per 100,000 contributed by passive smoking are then 0.27 (0.45 × 0.6) for the home and 1.1 (1.82 × 0.6) for the workplace. Application of these figures to the numbers of true and tainted controls and working and nonworking exposed women yields, after addition of the basal risk of 8.7 per 100,000, the figures shown in Table 6. The ratio of risks (all exposed:all controls) is then 1.03. Compared with the risk ratio in the Garfinkel (1981) study, this is a 14% difference. The lung cancer death rate for the weighted average of the "exposed" and "control" categories is 9.3 per 100,000, a 30% difference from Garfinkel's result.

When the one-hit model is used, the ratio of "all-exposed" to "true" controls is 1.09, a 38% difference with Hirayama's ratio. The corresponding lung cancer mortality rate is 9.45, a 39% difference with Hirayama's result.

Finally, using the phenomenological exposure-response relation, the ratio for "all exposed" and "true" controls is 1.7. Hirayama's (1981) average risk ratio was 1.78 from passive smoking, a 4.5% difference. Furthermore, if lung cancer risk rate calculation is performed with the tainted controls included as an exposed group, the result is 14.8 per 100,000, compared with Hirayama's observed 15.5 per 100,000, a 4% difference. In other words, the effect of moving the confounding tainted controls from Garfinkel's control group into his exposed group is to yield results within 5% of Hirayama's.

Thus, on the basis of this sensitivity analysis, it would appear that the phenomenological exposure-response relationship is better able to describe the results of the Garfinkel (1981) study than the one-hit model, and in addition, also appears to be able to explain quantitatively why the two large prospective studies of passive smoking and lung cancer yielded different results.

Table 5. Calculated lung cancer risks for each subgroup in the Garfinkel (1981) study using the 5 LCDs/100,000 person-yr/mg/day exposure-response relation.

Group	Rate
True controls	8.7
Tainted controls	17.8 (8.7 + 9.1)
All controls (weighted mean)	12.16
Exposed workers	20.05 (8.7 + 2.25 + 9.10)
Exposed nonworkers	10.95 (8.7 + 2.25)
All exposed (weighted mean)	14.41

Table 6. Calculated lung cancer risks for each subgroup in the Garfinkel (1981) study using the 0.6 LCDs per 100,000 person-yr/mg/day exposure-response relation.

Group	Rate
True controls	8.7
Tainted controls	9.8 (8.7 + 1.1)
All controls (weighted mean)	9.11
Exposed workers	10.07 (8.7 + 0.27 + 1.1)
Exposed nonworkers	8.97 (8.7 + 0.27)
All exposed (weighted mean)	9.39

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Table 7. Comparison of estimated risks from various hazardous air pollutants. Risks have been assessed for non-occupational exposures of the general population to several hazardous air pollutants. All are airborne carcinogens; all but passive smoking are being regulated by society. The statistical mortality given is before control.

Pollutant	Estimated Annual Mortality[a,b]	Reference
Passive smoking	5000 LCDs per yr	(this work)
Vinyl chloride	<27 CDs per yr	(U.S. EPA, 1975)
Radionuclides (worldwide impact from Department of Energy facilities)	17 CDs per yr	(U.S. EPA, 1983b)
Coke oven emissions	<15 LCDs per yr	(U.S. EPA, 1984)
Benzene	<8 CDs per yr	(U.S. EPA, 1979b)
Arsenic	<5 LCDs per yr	(U.S. EPA, 1980)

[a]CD = cancer death; LCD = lung cancer death.
[b]Risks for passive smoking and radionuclides are best estimates, and risks for other pollutants are upper bound.

Comparison of the Estimated Risk of Passive Smoking with those of Hazardous Air Pollutants Currently Under Regulation

Although the quantitative estimates presented should be regarded as preliminary and subject to confirmation by further research, the evidence suggests that passive smoking appears to be responsible for about one-third of the annual lung cancer mortality among U.S. nonsmokers. To place these estimates in perspective, Table 7 gives a comparison of the estimated risk of passive smoking to risks estimated by the U.S. Environmental Protection Agency for the carcinogenic hazardous air pollutants currently regulated under section 112 of the Clean Air Act (SCEP, 1977). As Table 7 demonstrates, passive smoking appears to pose a public health risk larger than the hazardous air pollutants from all regulated industrial emissions combined.

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Appendix A: Modeling Exposure of Nonsmoking U.S. Adults to Ambient Tobacco Smoke

Introduction

Lifestyle is the integrated way of life of an individual; aspects of lifestyle which will be considered here have to do with the amount of time a nonsmoker spends in contact with smokers, and therefore with their effluent. Exposure of nonsmokers to tobacco smoke might be expected to be common in the United States because one out of three U.S. adults smokes cigarettes at the estimated rate of 32 per day (Repace and Lowrey, 1980), and an additional one out of six smokes cigars or pipes. Furthermore, indoor air pollution from tobacco smoke persists in indoor environments long after smoking ceases (Repace and Lowrey, 1980, 1982).

Earlier work (Repace and Lowrey, 1980) presented a model of nonsmokers' exposure to the particulate phase of ambient smoke which was supported by controlled experiments and field survey of the levels of respirable particles indoors and out, in both smokefree and smoky environments. This work, which established that ambient tobacco smoke imposed significant air pollution burdens on nonsmokers, was extended by later work (Repace and Lowrey, 1982) that further demonstrated the predictive power of this model. The model predicts a range of exposure of from 0 to 14 mg of cigarette aerosol per day, depending upon the nonsmoker's lifestyle. Exposures of prototypical nonsmokers were modeled, but no attempt was made to estimate the average population exposure. Concentrations of ambient tobacco smoke encountered by nonsmokers can be approximated by equilibrium values that are determined by the ratio of the average smoker density to the effective ventilation rate (Repace and Lowrey, 1980, 1982); in practice, design ventilation standards based on occupancy are useful surrogates for effective ventilation rates. On the average, a characteristic value of this ratio can be assigned to a particular microenvironmental class, e.g., homes, offices, restaurants, etc. (Repace *et al.*, 1980). Therefore, the average daily exposure of individuals can be estimated from the time-weighted sum of concentrations encountered in various microenvironments containing smoke (Ott, in press; NRC, 1981; Szalai, 1972; Repace *et al.*, 1980).

Exposure and lifestyle

It is important to realize that most persons' lifestyles are such that they spend nearly 90% of their time in just two microenvironmental classes, thus affording a great simplification of exposure modeling. Szalai (1972), as part of The Multinational Comparative Time Budget Research Project, which studied the habits of nearly 30,000 persons in 12 countries (from 1964 to 1966), has compiled data reporting the average time spent in various locations or microenvironments. The data for 44 cities in the United States, as analyzed by Ott (in press) are summarized in Table A1 (see also NRC, 1981).

Table A1 shows that U.S. urban people spend an average of 88% of their time in just two microenvironments: in homes and workplaces. Moreover, employed persons in the U.S. cities are estimated to spend only 3% of the day outdoors, while housewives spend only 2% outdoors (Ott, in press; NRC, 1981). Assume that these values are representative of the entire population. [In 1970, approximately three fourths of the population was urban (USDC, 1980).]

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Table A1. Time spent in various microenvironments by persons in 44 U.S. cities, expressed in average hours per day. (Ott, in press; NRC, 1981; Szalai, 1972).

Microenvironment	Employed Men, All Days	Employed Women, All Days	Married Housewives, All Days
Inside one's home	13.4	15.4	20.5
Just outside one's home	0.2	0.0	0.1
At one's workplace	6.7	5.2	–
In transit	1.6	1.3	1.0
In other people's homes	0.5	0.7	0.8
In places of business	0.7	0.9	1.2
In restaurants and bars	0.4	0.2	0.1
In all other locations	0.5	0.3	0.3
Total	24.0	24.0	24.0

Modeling exposure of nonsmokers at work

Exposure of the population to the particulate phase of cigarette smoke can be modeled to determine both range of exposure and the nominal inhaled dose, which is exposure multiplied by the respiration rate (Altman and Dittmer, 1971).

Repace and Lowrey (1980, 1982a) have shown that the ambient concentration of tobacco smoke particles, Q, from cigarette smoking can be usefully represented by an equilibrium model of the form $Q = 650\ D_c/C$, where D_c is the number of burning cigarettes per 100m³, and C is the ventilatory air exchange rate in air changes per hour (ach). Rewriting this in terms of the occupancy of the space by habitual smokers (Repace and Lowrey, 1980) (for every 3 habitual smokers, there is one cigarette burning constantly), D_h($= 3D_c$):

$$Q = 217\ D_h/C, \quad (\mu g/m^3), \qquad (A1)$$

where D_h is the habitual smoker density in units of smokers per 100 m³, and C is the air change rate in units of air changes per hour (ach). Because The American Society of Heating, Refrigerating, and Ventilating Engineers (ASHRAE) (Leaderer *et al.*, 1981), sets consensus standards for ventilation rates in the United States, and because those standards are tied to expected building occupancy (e.g., ASHRAE, 1981), Eq. (A1) offers the possibility of modeling the range of nonsmokers' exposures by estimating the ranges of occupancy and air change rate. Appendix A1 estimates that the average annual exposure to ambient tobacco smoke particles by a typical nonsmoking U.S. worker is 1.8 mg/day, with an exposure probability of 63%.

Modeling exposure of nonsmokers at home

By reviewing data from time budget and census studies, the average length of time a person spends in the home microenvironment can be calculated. This time differs for gender and employment status. Taking into account the different amounts of time spent in the home by employed men, employed women, and homemakers, an estimate of occupancy-weighted average number of cigarettes smoked in the home during a 16-h waking day can be made. If the entire waking day is spent at home, 32 cigarettes per day (CPD) are smoked in the house by a smoker of either sex. An estimated occupancy-weighted average number cigarettes equal to 22 CPD smoked in the typical home is derived in Appendix A2. Using Eq. (A1), multiplied by the ratio 22/32, times a 1 m³/h respiration rate for a 16-h period, the calculation is made for a single-family detached dwelling of 340 m³ volume (see Appendix A3), assuming that on a 16-h basis, the entire finished volume of the home is available for dispersion of the smoke. A typical nonsmoker of either sex appears to be exposed to an average inhaled dose of 0.45 mg/day, assuming that occupancy of the home by smokers and nonsmokers is coincident.

Mean estimated dose to a typical adult from the most-frequented microenvironments

A probability-weighted average exposure to a hypothetical typical U.S. adult is estimated by combining the estimated dose to U.S. adults exposed in the workplace and at home, and by weighting the exposure received in each microenvironment by the probability of receiving it. Appendix A1 estimates that nonsmoking U.S. workers are exposed on the job to tobacco smoke with a probability of 63%. Appendix A2 estimates that nonsmoking U.S. adults are exposed at home to tobacco smoke with a probability of 62%. Table 1 (main text) gives the combinations of these probabilities, assuming that they are independent, i.e., that exposure at work is not correlated to exposure at home. Table 1 suggests that only a relatively small percentage (14%) of the population may escape daily passive smoke exposure. By contrast, individuals having exposure both at home and at work constitute a high exposure group, with the workplace likely contributing more exposure than the home by a ratio of 4 to 1.

On the basis of Table 1 it is estimated that the mean daily exposure of nonsmoking U.S. adults to tobacco tar and nicotine from the breathing of indoor air contaminated by cigarette smoke is about 1.43 mg/day, averaged over the two most-frequented microenvironments. This may be compared to the estimate of 14 mg/day to the hypothetical most-exposed individual (Repace and Lowrey, 1980). These results indicate that the typical U.S. "nonsmoker" appears to be exposed to a finite, non zero amount of tobacco aerosol, equivalent in value to three low-tar cigarettes (0.55 mg) per day.

In summation, it is possible, based on ASHRAE standards, time budget, and census surveys, the physics of indoor air pollution transport, and tables of respiration rates, to estimate the average exposure of a typical nonsmoking U.S. adult of working age. Using this methodology, estimates of the average exposure of the U.S. adult population of working age to the particulate phase of ambient tobacco smoke are made for the two most-

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frequented microenvironments: the workplace and the home. It is estimated that 86% of adults of working age are exposed to ambient tobacco smoke on a daily basis, and 14% are not. It is estimated that the range of exposure varies from 0 to 14 mg of tobacco tar per day, and that the typical exposure, averaged over 100% of the population, is 1.43 mg/day. It also is estimated that those individuals who are exposed both at home and at work receive a daily average exposure of 2.4 mg/day, and that 39% of the adult worker population is in this category. Those individuals exposed *only* at home receive a daily exposure of 0.5 mg/day, and that 23% of the adult population is in this category. Finally, it is estimated that those individuals exposed *only* at work receive a daily exposure of 1.8 mg/day, and that 24% of the worker population is in this category. Thus these estimates suggest that the ratio of workplace dose to the exposure received at home is nearly 4:1, indicating that, on the average, the workplace is a more important source of exposure than the home environment. Consistency of these estimates of workplace and domestic exposure with field data is given in Appendices A1 and A2.

Appendix A1: Modeling the Average Daily Exposure to Cigarette Smoke for a Typical U.S. Nonsmoking Worker

It is possible to arrive at an estimated aggregate exposure because the range of occupancies (i.e., smoker densities) is tied to the range of ventilation rates, which in turn determine the range of concentration of ambient tobacco smoke to which nonsmokers are exposed. A form of Eq. (A1) is given that can be related directly to the ASHRAE Standards 62-73 (ASHRAE, 1973), promulgated in 1973, which set standards for natural and mechanical ventilation. The practical range of occupancy given in the ASHRAE Standard 62-1973 is from 5 persons/1000 ft² to 150 persons/1000 ft² (5.4 P/100 m² to 161 P/100 m²), for commercial and institutional buildings.

From 1946 to 1973, the operable engineering standard was descriptive of general practice rather than prescriptive: The American Standard Building Code Requirements for Light and Ventilation A53, Section 8 (ASA, 1946) described typical practice for mechanical ventilation based on floor area, not occupancy. Section 8 described minimum values of 0.5 CFM/ft² for offices, 1 to 1.5 CFM/ft² (4.4 to 6.6 L/s m²) for workrooms, and a range of 0.05 to 3 CFM/ft² (2.2 to 13.2 L/s m²) for public and institutional buildings, with the lower value applying to museums, and the upper value to dance halls. This implies air exchange rates varying from 3 to 18 ach, and at the maximum of 75% recirculation described, this range reduces to 0.75 to 4.5 ach. In 1970, 60.7% of the U.S. workforce worked in the white-collar and service occupations that inhabit such buildings (USDC, 1980). A 1979 survey of 3000 employers in large, medium, and small corporations indicated that smoking was prohibited in only 10.5% of white-collar workplaces and in 27.5% of blue-collar workplaces (NICSH, 1978). These percentages would likely have been less in 1970. Equation (A2) expresses the concentration, R, as a function of occupancy, which is now a surrogate (Repace and Lowrey, 1978, 1982a) for smoker density:

$$R = 25.6\, P_o/C_v \quad (\mu g/m^3), \qquad (A2)$$

where P_o is the occupancy in persons per 1000 ft² [100 m²], and C_v is the ventilatory air change rate in ach, as before. Exposures can be calculated by multiplying R by the integrated average respiration rate expected for an adult nonsmoker over an 8-h workday. A reasonable value is 8 m³ per workshift, a value corresponding to alternate sitting plus light work (Table A2). Multiplying Eq. (A2) by this rate yields the equation for the amount of tobacco tar inhaled, N_d:

$$N_d = 0.205\, P_o/C_v \quad (mg/8\,h), \qquad (A3)$$

where the other parameters are defined as in Eq. (A2). ASHRAE Standards 62-73 yield the ranges in P_o of 5 to 150 and in C_v of 0.15 to 18 ach.

Table A3 expresses the variation of these parameters from the absolute minimum airchange rate to the recommended minimum and maximum rates, and enables us to bound the modeled dose for the workplace. The extreme bounds of workplace exposure can be estimated to range from $1.35 \leq N_d \leq 6.77$ mg/8 h. This assumes that one-third of the occupants are smokers [following the U.S. average that one-third of the adult population smokes (USSG, 1979)], and that they smoke sales-weighted-average tar cigarettes at the rate of 32 per 16-h day (Repace and Lowrey, 1980). Clearly, the true minimum bound is zero, and the maximum exposure may be higher due to the presence of chainsmokers or a higher than average number of smokers, but what is desired is an expected average value for the workplace exposure. At the ASHRAE-recommended minimum ventilation, the upper bound for N_d will be 3.38 mg/8 h. Thus, the probable average range for N_d is between 1.35 and 3.38 mg/8 h. The average of these two figures, $N_d = 2.37$ mg/8 h, represents the mean exposure for U.S. workers who are on-the-job passive smokers. This value may be

Table A2. Range of typical adult respiration rates for different levels of effort after Altman and Dittmer (1971).

Activity Level	Respiration Rate (m³/h)
Resting	0.36
Sitting	0.60
Alternate Sitting & Light Work	0.99
Light Work	1.47
Heavy Work	2.04

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Table A3. Calculation of the range of concentration Q, and exposure N_e to which nonsmokers are subject under the model given by Eqs. (A2) and (A3) assuming ASHRAE standard ventilation.

Occupancy	P_o [occupants per 1000 ft² (per 100 m²)]	C_r [airchanges/hour (ach)]	N_e Exposure (mg/8 h)	Q Concentration (μg/m³)
A Using ASHRAE 62-73 recommended maximum makeup air based on occupancy				
Maximum	150	18	1.69	213
Minimum	5	0.5	2.03	256
Offices	10	1.5	1.35	170
B Using ASHRAE 62-73 absolute minimum makeup air based on occupancy				
Maximum	150	4.5	6.77	853
Minimum	5	0.15	6.77	853
Offices	10	0.3	6.77	853
C Using ASHRAE 62-73 recommended minimum makeup air based on occupancy				
Maximum	150	9	3.38	655
Minimum	5	0.3	3.38	655
Offices	10	0.9	2.26	284

transformed into a daily average using Table A1. In 1972, (USDC, 1980) 38% of the workforce was female: 0.38 × (5.2 workhours/day) and 62% was male: 0.62 × (6.7 workhours/day); the sum of these is 6.13 workhours/day, daily average. Thus, the daily average exposure is N_e = (6.13/8) × 2.37 = 1.82 mg/day.

It now remains to estimate the percentage of workers who are exposed to cigarette smoke at work. The National Interagency Council on Smoking and Health conducted a survey of top management and health officials of 3000 U.S. corporations in 1978 (NICSH, 1978). A 29% response rate was achieved. The survey indicated that of blue-collar companies surveyed, 30.6% had no restrictions on smoking, 42% permitted smoking in designated areas, and 27.5% completely prohibited smoking. The corresponding percentages for the white-collar companies were, respectively, 74.3%, 15.2%, and 10.5%. Smaller companies were less likely to have restrictions. Among companies with restrictions, about one-half imposed penalties for violations. In addition, 63% of the respondents indicated that their policy was established after the release of the 1964 Surgeon General's Report on Smoking.

In 1970, white-collar workers constituted 48.3% of the workforce, blue-collar workers 35.3%, service workers 12.4%, and farmworkers 4% (USDC, 1980). The largest change in any category from 1960 to 1979 was that of white-collar workers, increasing by 7%. Since about one-half of the blue-collar companies imposed penalties for smoking, it will be assumed that 50% of the blue-collar nonsmokers were not exposed on the job. By contrast, it will be assumed that only 25% of the white-collar workers were not exposed. It will further be assumed that one-half of all workers follow white-collar smoking rules, and the other half, consisting of blue-collar workers, service workers, and farmworkers, follow blue-collar rules. Thus, the estimated weighted average percent of nonsmoking workers who are significantly exposed to tobacco smoke on the job is: 0.50 × 50% + 0.75 × 50% = 62.5%. By comparison, a 1983 survey of 1515 white-and blue-collar businesses sampled at random reported that "nearly two-thirds" had no smoking restrictions in the workplace (Tobacco Institute, 1984).

At this stage it must be asked whether the numbers calculated are reasonable in terms of measurements of ambient tobacco smoke under natural conditions. Repace and Lowrey (1980, 1982a), in a field survey of ambient tobacco smoke in 23 commercial buildings in the metropolitan Washington, D.C., area during 1979–1980, found concentrations ranging from about 100 μg/m³ to more than 1000 μg/m³. This range is quite compatible with the concentrations Q derived in Table A3. The average of all values measured under a variety of smoking conditions and ventilation rates by Repace and Lowrey was 242 μg/m³ (range 100 to 1000 μg/m³) for these 23 locations, corrected for background. This is compatible with the values calculated in Table A3. Breathing 242 μg/m³ of ambient tobacco smoke for 8 h at a rate of 0.99 m³ h yields an exposure of 1.92 mg/8 h or on a daily average basis, 1.92 × (6.13/8) = 1.47 mg.

In terms of relative exposures, these results also appear to be reasonable. In Appendix A2, an average smoking rate of 32 CPD was used (Repace and Lowrey, 1980). At current sales-weighted average tar plus nicotine values (14 mg) (USFTC, 1984), the typical smoker would inhale (14 mg/cig) × 32 CPD = 448 mg/day. In Table 1, the typical passive smoker was calculated to inhale 1.43 mg/day. This is a relative exposure ratio of 313:1. Wald *et al.* (1984a), in a study of urinary cotinine levels in smokers and nonsmokers, found the ratio (1645 ng/mL)/(6 ng/mL) = 274:1. Thus, the ratio of exposures calculated theoretically using the model derived here differs by only 14% from an experimentally derived value based on a biological marker of exposure.

Appendix A2. Calculation of the Estimated Daily Average Number of Cigarettes Smoked in the Average Home

Since the source strength depends upon the length of time smokers spend in indoor microenvironments, it is necessary to review pertinent information from time budget (Ott, in press; Szalai, 1972; NRC, 1981) and census (USDC, 1980) studies, which gives the average length of time that persons spend in various microenvironments.

From Table A1, it is seen that, allowing for 8 h of sleep, employed men spend 34.4% of the waking day in

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the home; employed women spend 45.9% of the waking day in the home; "housewives" spend 81% of the waking day in the home. In 1979, approximately 42% of families with both the husband and wife present, both were employed. Thus for homes occupied by married couples, 66% of the waking day (weighted mean averaged over 42% working wives and 58% homemakers) the home is occupied by a wife, and 34% of the day, by a husband. If the average habitual smoker smokes 32 cigarettes per day (CPD), then the wife will smoke 21 CPD in the house, and the husband will smoke 11 CPD in the house.

Bonham and Wilson (1981) found that 62% of U.S. homes with children in 1970 contained one or more smokers, and 25% contained two or more. Thus we may assume that of homes with one or more smokers, 40% have two smokers, and 60% have one smoker. We have three cases to consider: (a) Husband and Wife Both Smoke, (b) Only Wife Smokes, and (c) Only Husband Smokes. In 40% of the smoking homes, case (a) is true, and in 60% of those homes, either cases (b) or (c) is true. Specifically, 38% of men and 30% of women smoke (US DHHS, 1979). Then the probability of case (c) being true is 34% (38/68 × 60%), and the probability of case (b) being true is 26% (30/68 × 60%). The weighted mean of these is given by the sum of the products of the percent of homes with a given number of smokers of either or both sexes, times the number of cigarettes per day smoked by either or both sexes: 0.40 × 32 + 0.26 × 21 + 0.34 × 11 = 22 CPD, estimated to be smoked daily in the average U.S. home, or about a pack per day. Is this theoretical estimate a reasonable number?

Dockery and Spengler (1981a, 1981b), in a 1-yr study of indoor air pollution in 68 homes in 6 U.S. cities, found that cigarette smoking was the dominant source of respirable particles (RSP); in a typical house in the study, the average 24-h RSP levels were increased by 0.88 $\mu g/m^3$ per cigarette smoked, and in a tightly sealed house, by a value of 2.11 $\mu g/m^3$. At an estimated occupancy-weighted average in-the-home smoking rate of 22 cigarettes per day, a 24-h average RSP level of about 19 $\mu g/m^3$ (22 CPD × 0.88 $\mu g/m^3$ CPD) is calculated for the typical house; in fact, Spengler *et al.* (quoted in NRC, 1981) observed a 24-h average of 19 $\mu g/m^3$ in 22 of the homes in the study where there was only 1 smoker. This number corresponds to an air exchange rate of 1.5 ach using the model (see Appendix A3). Since this air exchange rate is within the expected range (Repace and Lowrey, 1980, 1982), an average of 22 CPD smoked in the home provides a reasonable basis for estimating exposure.

The theoretical in-the-home number of cigarettes smoked in the home is weighted for occupancy during the waking day. Since there is no data differentiating occupancy for smokers and nonsmokers, it is assumed that the statistical occupancy of the nonsmoker is coincident with that of the smoker, i.e., that there is a nonsmoker present to receive the exposure. In order to calculate the daily dose received, Eq. (A1) is used with the parameters D_s = 0.29 smokers/100m^3, C_r = 1.5 ach, times an occupancy factor of 22/32, times a respiration rate of 0.99 m^3/h, times a 16-h maximum exposure day, yielding an estimated average exposure of 0.45 mg/day, for an adult nonsmoker, with an exposure probability of 62%.

A reasonable approximation to the probability of a typical nonsmoking adult being exposed to ambient tobacco smoke at home is 62%, the same as Bonham and Wilson (1981) above found for adults with children (in 1970, 56% of families had one or more children under 18) (USDC, 1980). No differentiation is made between male and female nonsmokers, since Friedman *et al.* (1983) observed that degree of passive smoking had little correlation with gender. In households with 2 or more smokers, there might not be an adult nonsmoker to be exposed; in this case, the probability of passive smoking (for a nonsmoker) reduces from 62% to 37%. However, the estimated total exposure (Table 1) only decreases by 8%, from 1.43 to 1.34 mg/day. In the absence of data on this point, it will be assumed that a nonsmoking adult is present.

Appendix A3. Calculation of the Ratio of the Habitual Smoker Density to the Air Exchange Rate for a Typical U.S. Single Family House

The typical range of annual closed-window air exchange rates in U.S. residences is generally considered to be of the order of 0.5 to 1.5 ach, with the range for the average residence of the order of 0.7 to 1.1 ach, and that of the tighter and newer residences of the order of 0.5 to 0.8 ach (Fuller, 1981). So-called energy-efficient structures have rates of the order of 0.3 to 0.5 ach. (Repace, 1982). A typical U.S. single-family detached house is estimated to have a floor area of 1500 $ft.^2$ [139 m^2] with an 8-ft [2.4-m] ceiling, for a volume of 340 m^3 (NAHB, 1981).

Thus, per habitual smoker, the ratio D_s/C_r = (1/3.4)/1.0 = 0.29 habitual smokers per hundred cubic meters per air change per hour. In 1978, nearly ⅔ of occupied housing units were single-family detached dwellings (USDC, 1980). It is assumed that the ratio calculated above is valid for multifamily dwellings as well (the volume of an apartment in a multifamily building is likely to be less, but the air exchange rate is likely to be greater).

Appendix B: Extrapolated Estimate of Risk From Passive Smoking

An alternative method of estimation of risk from passive smoking is calculated as follows. In 1980, 108,504 individuals in the United States were reported

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to have died from lung cancer (USPHS, 1983). The 1982 Surgeon General's report on Smoking and Cancer estimated that 85% of LCDs are due to cigarette smoking (USSG, 1982); this yields 92,228 LCDs/yr. Lung cancers occur primarily in smokers over the age of 35 (NCI, 1966); in 1980, there were an estimated 29,225,000 smokers of all races and both sexes in this age bracket (USPHS, in press). It follows that in 1980, there were 3.156×10^{-3} LCDs per smoker of lung cancer age. In 1978 the average cigarette was 17 mg tar, and the average smoker smoked 32 cigarettes per day (Repace and Lowrey, 1980), for an estimated tar intake of 544 mg/day-smoker. (A 1980 lung cancer death reflects a 20- to 40-yr smoking history, during which smoking rates increased by, and tar levels decreased by, about 50% (USSG, 1979). Thus, 3.156×10^{-3} LCDs/smoker divided by 544 mg/day-smoker yields a rate of about 5.8×10^{-6} LCDs/yr per mg/day per smoker of lung cancer age.

Using a one-hit model (Hoel *et al.*, 1983; Crump, 1976) for the extrapolation of the risk from the estimated exposure of smokers down to the estimated exposure of nonsmokers provides an alternate exposure-response relationship. Crouch and Wilson (1981) have used this model, which saturates at high exposures, but which is linear at low exposures. This model has the form $P(D) = 1 - \exp(bD)$, where $P(D)$ is the estimated risk, b is the exposure-response function, and D is the exposure. The one-hit model, because of its functional form, can be considered as the first stage of the more complex multistage model. (U.S. EPA, 1983a; Hoel *et al.*, 1983) Whenever the data can be fitted adequately by the one-hit model, estimates of both models will be comparable (U.S. EPA, 1983a; Crump, 1976; Hoel *et al.*, 1983).

From above, $b = 5.8 \times 10^{-6}$ LCDs per year per mg/day. $D = 1.5$ mg/day, from the estimated average exposure for the typical U.S. nonsmoker (Appendix A), assuming that per milligram, tobacco tar produces the same carcinogenic response in nonsmokers as it does in smokers. This calculation yields an estimated annual LCD risk about 0.87×10^{-3} from passive smoking, or about an order of magnitude lower than the phenomenological estimate made earlier. In this exposure range, this result is essentially the same as would be obtained from a linear extrapolation.

The primary age group at risk of lung cancer is that $\geq$ 35 yr (Reif, 1981a, 1981b). Therefore, in the calculation that follows only nonsmokers $\geq$ 35 yr will be assumed to be at risk of lung cancer. In 1980, there were about 63.8 million nonsmokers aged $\geq$ 35 (USPHS, in press). Thus, the alternative risk estimate is derived from multiplying 0.87 LCDs/yr per 100,000 passive smokers times 63.8×10^{4} passive smokers at risk, yielding 555 LCDs per year in U.S. nonsmokers from passive smoking, using the one-hit model of carcinogenesis for extrapolation.

Appendix C: Age-Standardized Calculation of Estimated Annual U.S. Mortality and Loss of Life Expectancy From Involuntary Exposure to Ambient Tobacco Smoke

Approximately 50% of SDAs in the cancer age range (>35 yr old) are adult converts to the church; others were either born into an SDA home or joined the church prior to age 20, typically with other immediate family members. A large proportion of SDAs tend to be heavily involved in church activities. Only a small proportion of SDAs report current use of cigarettes (males, 1.7%; females 0.5%) (Phillips *et al.*, 1980b). (By contrast, in 1970, 43.5% of adult males and 31.1% of adult females in the general population aged $\geq$ 17 yr reported smoking) (USDHHS, 1979).

Moreover, a substantial portion of SDAs work for "an organization owned and operated by the SDA Church" [nearly 45% of SDA females and 40% of SDA males in the study group (aged $\geq$ 25 yr), reported working for the SDA Church.] (Phillips *et al.*, 1980a, 1980b). Clearly, SDAs are less likely than the general population to be involuntarily exposed to tobacco smoke, as children or as adults, at home or in the workplace, because neither SDA homes nor SDA businesses are likely to be places where smoking is permitted, and because the great majority of SDA family and social contacts are among other SDAs who do not smoke (Phillips *et al.*, 1980b).

Table C1 shows the age-standardized calculation of estimated loss of life expectancy and annual lung cancer mortality from passive smoking. The calculation is based on the lung cancer mortality difference between two Southern California cohorts of self-reported nonsmokers who never smoked. Based on lifestyle differences, they appear to have different average levels of involuntary smoke exposure. The more-exposed group are designated non-SDAs, and the less-exposed group SDAs (see main text).

Columns 1, 2, 5, and 6 are tabulations from which age-adjusted mortality rates were calculated in the study of mortality in the Seventh-Day Adventist (SDA) by Phillips *et al.* (1980a, 1980b). Columns 1 and 2 and 5 and 6 give the age-specific lung cancer deaths and person-years at risk, respectively, for the SDA and the non-SDA. The fractional number of LCDs in column 1 is due to a correction for out-migration of the SDA population from the study area.

Columns 3, 7, 10, and 11 show the average numbers of individuals at risk annually during the study, allowing for those who died during the study. Columns 4 and 8 show the annual average lung cancer death rate (LCD) per 100,000 persons, and column 9 gives the differences between the non-SDAs and SDAs in those rates. Column 12 gives average LCD rates weighted to reflect the fact that there were three times as many women as men in the study, and that the female data attained statistical significance whereas the male did not—although the

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combined data were significant (Phillips *et al.*, 1980a, 1980b). A common LCD rate is assumed for both sexes in the calculation that follows. Also, it will be assumed that the entire LCD rate difference is due to passive smoking (see discussion on confounding factors in Appendix D).

Next, this calculation will be extrapolated to the entire U.S. nonsmoking population aged ≥ 35 yr. Column 13 gives the mean age of the individuals in the 5-yr age group, and column 14 gives the number of persons alive at that mean age per 100,000 born alive. Column 15 gives the total number of persons in the 5-yr age group (5 × column 14) per 100,000 born alive (whites only) from the 1974 U.S. Life Tables (USDHHS, 1975). Column 16 gives the age-specific LCD rates attributed to passive smoking, standardized to (i.e., weighted by) the age specific population distribution in 1974 for U.S. whites (column 12 times column 15).

Column 17 gives the average life expectancy corresponding to the mean age given in column 13, which is taken to represent that of the entire 5-yr age group. Column 18, the product of columns 16 and 17, gives the estimated age-specific age-standardized person-years of life lost due to lung cancer from passive smoking.

The sum of the values of column 18 gives an estimated 3932 person-yr of life lost due to passive smoking per 100,000 persons alive at age 35 in the U.S. population in 1979. 3932 person-yr, when divided by the 94,724 persons (USDHHS, 1975) at risk at age 40 (LCDs were not observed at earlier ages in the SDA study; however, they are observed in the general nonsmoking U.S. population at age 35) (USSG, 1979) yields 15 days, the mean number of days of life lost, and, multiplying by the peak-to-mean exposure ratio, 148 days for the maximum number of days lost (where the risks of the non-white population are taken to be the same as for the white population.)

Column 19 is column 16 times 62.424 million divided by the sum of column 15. The sum of column 19 gives an estimated age-standardized mortality total of 4,665 LCDs per year in U.S. nonsmokers from passive smoking (where there were 93,636,000 persons aged ≥ 35 yr

Table C1. Age-standardized estimation of lung cancer deaths from passive smoking.

Females

5 yr. Age Group	SDA Never Smokers 1. Total LCDs (17 yr period)	2. Person yr at Risk	3. Average Annual No. of Persons	4. LCDs per 100,000 Person Years	Non-SDA Never Smokers 5. Total LCDs (12.58 yr period)	6. Person yrs. at Risk	7. Average Annual No. of Persons at Risk	8 LCDs per 100,000 Person Yrs
35-39	0	3791	223.0	0	0	5766	458.3	0
40-44	0	11494	676.1	0	1	16466	1308.3	6.0731
45-49	0	18757.5	1103.4	0	2	38319	3046.9	5.2191
50-54	1.119	24808.5	1459.3	4.5106	4	61630	4899.0	6.4909
55-59	1.000	24702	1453.1	4.0483	8	71289	5666.9	11.222
60-64	1.101	24051.5	1414.8	4.5777	7	65054	5171.2	10.760
65-69	1.148	23326.5	1372.1	4.9214	4	55614	4420.8	7.1924
70-74	0	21809	1282.9	0	9	44248	3517.3	20.340
75-79	1.000	18822	1107.2	5.3219	10	29250	2325.1	34.188
80-84	7.775	13435.5	790.3	57.869	6	15301	1216.3	39.213
85+	2.258	10017.5	589.5	22.541	10	7891	627.3	126.73
Total	15.401	195,015	11,472	103.7899	61	410,828	32,657	267.428

Males

5 yr. Age Group	SDA Never Smokers				Non-SDA Never Smokers			
35-39	0	1926.5	113.0	0	0	1581	119.3	0
40-44	0	5732.5	337.2	0	0	3479	276.6	0
45-49	0	9177	539.8	0	0	9662	768.0	0
50-54	0	11480	675.3	0	1	19313	1535.2	5.1779
55-59	1.119	10359.5	609.4	10.8017	2	23848	1895.6	8.3863
60-64	1.000	8763.5	515.5	11.440	4	19535	1552.9	20.4761
65-69	3.401	7386.5	434.5	46.0435	8	14105	1121.2	56.7173
70-74	1.115	6360.5	374.1	17.5301	0	9786	777.9	0
75-79	0	5278.5	310.5	0	2	6541	520.0	30.5764
80-84	1.143	3957.0	232.8	28.8855	4	3517	279.6	113.733
85+	2.235	3160.0	185.9	70.7278	2	1671	132.8	119.669
Total	10.013	73581.5	4328.0	185.4286	23	113,038	8979.1	354.7564

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Table C1. (Continued).

5 yr Age Group	Females: 9. Annual LCDs per 100,000 (Non-SDA)-(SDA)	Females: 10. Average Age-Specific No. of SDA & Non SDA at Risk	Male/Female: 11. Average Age-Specific No. of SDA & Non SDA at Risk	Male/Female: 12. Annual Weighted Mean LCD per 100,000 (unisex)	13. Mean age of 5 yr Group	14. Mean No. of Persons At Risk at each yr of 5 yr Group	15. Mean No. of Persons At Risk in Entire 5 yr Age Group	16. Age Specific Age Stand (1974 U.S. White Population) LCDs
35-39	0	681	913	0	37.5	95,201	476,005	0
40-44	6.0731	1985	2599	4.64	42.5	94,122	470,610	21.84
45-49	5.2193	4149	5457	4.50	47.5	92,339	461,645	20.77
50-54	1.9803	6358	8569	2.81	52.5	89,590	447,950	12.59
55-59	7.1737	7120	9625	4.67	57.5	85,477	427,385	19.96
60-64	6.1823	6586	8654	6.87	62.5	79,396	396,980	27.27
65-69	2.2710	5793	7349	4.05	67.5	71,177	355,885	14.41
70-74	20.340	4800	5952	13.0	72.5	60,455	302,275	39.30
75-79	28.875	3432	4263	29.2	77.5	46,689	233,445	68.17
80-84	−18.656	2006	2518	2.35	82.5	31,209	156,045	3.67
85+	104.189	1217	1536	92.6	87.5	11,913	59,565	55.16
Total	163.6477	44,127	57,435	164.69	(1974 Census (whites per 100,000 at Birth)		3,787,790	203.14

5 yr. Age	Males: 9. Annual LCDs per 100,000 (Non-SDA)-(SDA)	Males: 10. Average Age-Specific No. of SDA & Non SDA at Risk
35-39	0	232
40-44	0	614
45-49	0	1308
50-54	5.1779	2211
55-59	−2.4152	2505
60-64	9.0651	2068
65-69	10.6740	1556
70-74	−17.5301	1152
75-79	30.5764	831
80-84	84.8475	512
85+	48.9612	319
Total	169.3568	13,308

Table C1. (Continued).

5 Yr. Age Group	17. Average life Expectancy for the 5-year Age Group	18. Person years of life lost due to LCDs from passive smoking	19. LCDs per year in age group in entire 1979 U.S. nonsmoking population aged ≥ 35 yr
35-39	—	0	0
40-44	33.1	723	360
45-49	28.7	596	343
50-54	24.6	310	207
55-59	20.8	415	329
60-64	17.2	469	449
65-69	14.0	202	237
70-74	11.1	436	647
75-79	8.6	586	1123
80-84	6.6	24	61
85+	3.1	171	909
	17 ± 9	3932	4665

in 1979, and two-thirds or 62,424,000 of these were nonsmokers).

Examining column 19, shows that of those individuals assumed to contract lung cancer from passive smoking, approximately 1½% do so at each year of age from 40 to 69, and over age 70, approximately 3% do so each year. Of those who actually contract fatal lung cancer from passive smoking, the mean life expectancy lost is about 17 ±9 yr, and about 8% lose as much as 33 yr.

Appendix D: Discussion of Confounding Factors

The IARC criteria for causality and human cancer specify that possible sources of bias and confounding error should be considered (IARC, 1979). What factors other than passive smoking could account for a lung cancer difference between two cohorts?

The most obvious one is misclassification. Some of the individuals classified as nonsmokers could have

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been smokers or exsmokers, giving rise to a spurious effect. Workplace or residential exposure to lung carcinogens or dietary differences between the cohorts might also give rise to spurious differences. However, this is not likely to be an effect constant over 14 positive studies in six different countries, all of which report about a doubling of risk when the exposure variable is spouses' smoking.

Arsenic, asbestos, beryllium, chloroethers, chromium, coke oven emissions, nickel, radon, and vinyl chloride, as well as tobacco smoke, have been implicated in the etiology of lung cancer (Ives, 1983; Selikoff, 1981). Possible differences due to industrial exposures should be expected primarily in blue-collar workers. Phillips *et al.* (1980a, 1980b) have stated that the SDA/non-SDA subgroups were demographically and educationally similar, suggesting similar occupational distributions, although there is no information on this point. There is no reason to believe that domestic radon levels, which are a property of the soil, would be any different in SDA homes than non-SDA homes. Finally, it should be considered that co-exposures to other lung carcinogens (e.g., radon) may increase the effect of passive smoking (Bergman and Axelson, 1983).

It is also possible that dietary differences between the two groups might have contributed to the SDA/non-SDA lung cancer difference. For example, 54% of SDAs follow a lacto-ovarian diet and 41% rarely use caffeine beverages. However, Hirayama (1981a, 1981b, 1983a, 1983b) observed a dose-response relationship between exposure to passive smoking and lung cancer even in those with an apparently cancer-inhibiting diet. Also, SDA/non-SDA cancer differences are not significant for other smoking-related cancer sites; this runs counter to a protective effect of diet as a confounding factor. Finally, Hirayama (1983a) observed that the magnitude of this effect varied from a mortality ratio of 1 for passive smoking women who did not follow a protective diet to 0.82 for women who use green-yellow vegetables only occasionally, to 0.72 for women who ate them daily. Thus the magnitude of the effect does not appear to be sufficient to account for the observed SDA/non-SDA lung cancer difference. Moreover, if 40% of the SDAs work for church-run organizations, 60% do not; these 60% surely must be subject to some passive smoking in the workplace, at least partially offsetting the effects of potential dietary or occupational differences with the non-SDAs.

References

Albert, R. E. (1983) discussion of APCA critical review paper on control of toxic substances in the atmospheric environment, *J. Air Pollut. Control Assoc.* 33, 836-837.

Anderson, E. L. (1983) Quantitative approaches in use to assess cancer risk, *Risk Anal.* 3, 277-295.

Altman, P. L. and Dittmer, D. S. (1971) Respiration and circulation. Federation of American Soc. for Experimental Biol., Bethesda, MD.

American Society of Heating, Refrigeration and Ventilation Engineers (1981) Ventilation for acceptable indoor air quality. ASHRAE Standard 62-1981, Atlanta, GA.

American Society of Heating, Refrigeration and Ventilation Engineers (1973) Standards for natural and mechanical ventilation. ASHRAE Standard 62-1973, New York, NY.

American Standards Association (1946) Light and ventilation. ASA 53, American Standards Association, New York, NY.

Bergman, H. and Axelson O. (1983) Passive smoking and indoor radon daughter concentrations, *Lancet* 2, 1308-1309.

Bock, F. G., Repace, J. L., and Lowrey, A. H. (1982) Nonsmokers and cigarette smoke: A modified perception of risk, *Science* 215, 197.

Bonham, G. S. and Wilson, R. W. (1981) Children's health in families with cigarette smokers, *Amer. J. Public Health* 71, 290-293.

Chan, W. C. and Fung, S. C. (1982) Lung cancer in non-smokers in Hong Kong, in *Cancer Campaign*, Vol. 6: *Cancer Epidemiology*, E. Grundmann, ed. Gustav Fischer Verlag, Stuttgart New York, NY.

Cohen, J. D. and Bartsch, G. E. (1980) A comparison between carboxyhemoglobin and serum thiocyanate as indicators of cigarette smoking, *Amer. J. Public Health* 70, 284-286.

Cohen, B. L. and Lee, I. (1979) A Catalog of risks, *Health Phys.* 36, 707-722.

Committee on Science and Tchnology (1983) A review of risk assessment methodologies. U.S. House of Representatives, 98th Congress, U.S. Govt. Printing Office, Washington, DC.

Correa, P., Pickle, L. W., Fonham, E., Lin, Y., and Haenszel, W. (1983) Passive smoking and lung cancer, *Lancet* 2, 595-597.

Crouch, E. and Wilson, R. (1981) Regulation of carcinogens, *Risk Anal.* 1, 47-57.

Crump, K. S., Hoel, D. G., Langley, C. H., and Peto, R. (1976) Fundamental carcinogenic processes and their implications for low dose risk assessment, *Cancer Res.* 36, 2973-2979.

Dockery, D. and Spengler, J. D. (1981a) Indoor-outdoor relationships of respirable sulfates and particles, *Atmos. Environ.* 15, 335-343.

Dockery, D. and Spengler, J. D. (1981b) Personal exposure to respirable particulates and sulfates, *J. Air Pollut. Control Assoc.* 31, 153-159.

Doll, R. and Peto, R. (1981) *The Causes of Cancer*, Oxford University Press, New York, NY.

Enstrom, J. E. and Godley, F. H. (1980) Cancer mortality among a representative sample of nonsmokers in the United States during 1966-68, *J. Natl. Cancer Inst.* 65, 1175-1183.

Enstrom, J. E. (1978) Cancer and total mortality among active mormons, *Cancer* 42, 1943-1951.

Fischoff, B., Lichtenstein, S., Slovic, P., Derby, S., and Keeney, R. (1981) *Acceptable Risk*. Cambridge University Press, Cambridge.

Friedman, G. D., Petitti, D. B., and Bawol, R. D. (1983) Prevalence and correlates of passive smoking, *Am. J. Public Health* 73, 401-405.

Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking, *J. Natl. Cancer Inst.* 66, 1061-1066.

Garfinkel, L. (1980) Cancer mortality in nonsmokers: Prospective study by the American Cancer Society, *J. Natl. Cancer Inst.* 65, 1169-1173.

Gillis, C. R., Hole, D. J., Hawthorne, V. M., and Boyle, P. (1983) The effect of environmental tobacco smoke in two urban communities in the west of Scotland, Proceedings, ETS—Environmental tobacco smoke; Report from a Workshop on effects and levels, March 15-17, Univ. of Geneva.

Hammond, E. C. and Selikoff, I. J. (1981) Passive smoking and lung cancer with comments on two new papers, *Environ. Res.* 24, 444-452.

Heller, W. D. (1983) Lung cancer and passive smoking, *Lancet* 2, 1309.

Hirayama, T. (1974) Prospective studies on cancer epidemiology based on census population in Japan, Proc. XI International Cancer Congress, October 20-26, Florence.

Hirayama, T. (1983a) Passive smoking and lung cancer: Consistency of association, *Lancet* 2, 1425-1426.

Hirayama, T. (1983b) Passive smoking and lung cancer, Proc. 5th World Conference on Smoking and Health, July 10-15, Winnipeg. In press.

Hirayama, T. (1981a) Nonsmoking wives of heavy smokers have a

2023381931

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higher risk of lung cancer: A study from Japan, *Brit. Med. J.* **282**, 183–185.
Hirayama, T. (1981b) Passive smoking and lung cancer, *Brit. Med. J.* **282**, 1393–1394.
Hoel, D. G., Kaplan, N. L., and Anderson, M. W. (1983) Implication of nonlinear kinetics on risk estimation in carcinogenesis, *Science* **219**, 1032–1037.
Hoel, D. G., Galyor, D. W., Kirschstein, R. L., Saffiotti, U., and Schneiderman, M. A. (1975) Estimation of risks of irreversible delayed toxicity, *J. Toxicol. Environ. Health* **1**, 133–151.
Interagency Regulatory Liaison Group (1979) Scientific bases for identification of potential carcinogens and estimation of risks: Report of the Work Group on Risk Assessment, *J. Natl. Cancer Inst.* **63**, 241–268.
International Agency For Research on Cancer (1979) Chemicals and industrial processes associated with cancer in humans, IARC Monographs, no. 5, 1–20, Suppl. 1.
Ives, J. C., Buffler, P. A., and Greenberg, S. D. (1983) Environmental associations and histopathologic patterns of carcinoma of the lung: The challenge and dilemma in epidemiologic studies, *Am. Rev. Respir. Disease* **128**, 195–209.
Jarvis, M. J. and Russell, M. A. H. (in press) Measurement and estimation of smoke dosage to non-smokers from environmental tobacco smoke, *Brit. Med. J.*
Kabat, G. C. and Wynder, E. L. (1984) Lung cancer in nonsmokers, Cancer, **53**, 1214–1221.
Kasuga, H. (1983) Hydroxyproline and passive smoking. Presented at New Etiologies in Lung Cancer Conference, March 21–23, Honolulu, Hawaii.
Kauffmann, F., Tessier, J. F., and Oriol, P. (1983) Adult passive smoking in the home environment: A risk factor for chronic airflow limitation, *Amer. J. Epidemiol.* **117**, 269–280.
Knoth, A., Bohn, H. and Schmidt, F. (1983) Passive smoking as a causal factor of bronchial carcinoma in female non-smokers, *Med. Klin.* **78**, 66–69.
Koo, L. C., Ho, J. H.-C., and Saw, D. (1983) Active and passive smoking among female lung cancer patients and controls in Hong Kong, *J. Exp. Clin. Cancer Res.* **4**, 367–375.
Lave, L. (1983) *Quantitative Risk Assessment in Regulation*. Brookings Institution, Washington, DC.
Leaderer, B. P., Cain, W. S., Isseroff, R., and Berglund, L. G. (1984) Ventilation requirements in buildings—II. Particulate matter and carbon monoxide from cigarette smoking, *Atmos. Environ.* **18**, 99–106.
Matsukura, S. *et al.* (1984) Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers—Evidence for passive smoking, *New England J. Med.* **311**, 828–832.
Meyer, B. (1983) *Indoor Air Quality*. Addison Wesley, Reading, MA.
Miller, G. H. (1984) Cancer, passive smoking and nonemployed and employed wives, *West. J. Med.* **140**, 632–635.
National Association of Homebuilders (1982) National Association of Homebuilders, Washington, DC.
National Cancer Institute (1966) Epidemiological approaches to the study of cancer and other chronic diseases, National Cancer Institute Monograph, no. 19.
National Interagency Council on Smoking and Health (1978) *Smoking and the Workplace*. Business Survey, NICSH, New York, NY.
National Research Council (1980) The effects on populations of exposure to low levels of ionizing radiation: 1980. National Academy Press, Washington, DC.
National Research Council (1983) Risk assessment in the federal government: Managing the process. National Academy Press, Washington, DC.
National Research Council (1981) Indoor pollutants. National Academy Press, Washington, DC.
Ott, W. R. (in press) Human activity patterns: A review of the literature for estimation of exposure to air pollution. U.S. Environmental Protection Agency, Washington, DC.
Pitot, H. C. (1981) *Fundamentals of Oncology*, 2nd ed. Marcel Dekker, New York, NY.
Phillips, R. L., Garfinkel, L., Kuzma, J. W., Beeson, W. L., Lotz, T., and Brin, B. (1980) Mortality among California Seventh-day Adventists for selected cancer sites, *J. Natl. Cancer Inst.* **65**, 1097–1107.
Phillips, R. L., Kuzma, J. W., Beeson, W. L., and Lotz, T. (1980) Influence of selection versus lifestyle on risk of fatal cancer and cardiovascular disease among Seventh-Day Adventists, *Amer. J. Epidemiol.* **112**, 296–314.
Reif, A. (1981a) Effect of cigarette smoking on susceptibility to lung cancer, *Oncology* **38**, 76–85.
Reif, A. (1981b) The causes of cancer, *Amer. Scientist* **69**, 437–447.
Repace, J. L. (in press) Risks of passive smoking, in *To Breathe Freely*, Center for Philosophy and Public Policy, University of Maryland, College Park, MD.
Repace, J. L. The dosimetry of passive smoking. 5th World Conference on Smoking and Health, July 10–15, 1983[a], Winnipeg.
Repace, J. L. (1983b) Effect of ventilation on passive smoking risk in a model workplace, in *Proceedings of an Engineering Foundation Conference on Management of Atmospheres in Tightly Enclosed Spaces, Oct. 17–21, Santa Barbara*, pp. 51–55. ASHRAE, Atlanta.
Repace, J. L. (1984) Consistency of research data on passive smoking and lung cancer, *Lancet* **2**, 506.
Repace, J. L. (1982) Indoor air pollution, *Environ. Int.* **8**, 21–36.
Repace, J. L. (1981) The problem of passive smoking, *Bull N. Y. Acad. of Med.* **57**, 936–946.
Repace J.L. and Lowrey, A. H. (in press) A proposed indoor air quality standard for ambient tobacco smoke. Proceedings of the 3rd International Conference on Indoor Air quality and Climate, August 20–24, 1984 Stockholm. *N.Y. State J. Med.*
Repace, J. L. and Lowrey, A. H. (1983) Modeling exposure of nonsmokers to ambient tobacco smoke. Proceedings of the 76th Annual Meeting of the Air Pollution Control Association, June 19–24, Atlanta.
Repace, J. L. and Lowrey, A. H. (1982) Tobacco smoke, ventilation, and indoor air quality *ASHRAE Trans.* **88**, 894–914.
Repace, J. L., Seba, D. B., Lowrey, A. H., and Gregory, T. W. (1983–1984) Effect of negative ion generators on ambient tobacco smoke, *J. Clin. Ecology* **2**, 90–94.
Repace, J. L. and Lowrey, A. H. (1980) Indoor air pollution, tobacco smoke, and public health, *Science* **208**, 464–472.
Repace, J. L., Ott, W. R., and Wallace, L. A. (1980) Total human exposure to air pollution. Proceedings of The 72nd Annual Meeting of the Air Pollution Control Assoc., June 22–27, Montreal.
Repetto, M. and Martinez, M. (1974) Benzopyrene de cigarettes et son excretion urinaire. *J. Europ. Toxicol.* **7**, 234–237.
Sandler, D. P., Everson R., B., and Wilcox, A. J. (in press, a) Passive smoking in adulthood and cancer risk, *Amer. J. Epidemiol.*
Sandler, D. P., Everson, R. B., Wilcox, A. J., and Browder, J. P. (in press, b) Cancer risk in adulthood from early life exposure to parents' smoking. *Am. J. Publ. Health.*
Sebkoff, I. J. (1981) Household risks with inorganic fibers, *Bull. N.Y. Acad. Med.* **57**, 947–961.
Senate Committee on Environment and Public Works (1977) U.S. Clean Air Act, As Amended August 1977. 95th Congress, 1st Session, Serial No. 95-11, U.S. Government Printing Office, Washington, DC.
Szalai, A. (1972) *The Use of Time: Daily Activities of Urban and Suburban Populations in Twelve Countries*. Mouton, The Hague Paris
Tager, I., Weiss, S. T., Munoz, A., Rosner, B., and Speizer, F. E. (1983) Longitudinal study of the effects of maternal smoking on pulmonary function in children, *N. England J. Med.* **309**, 699–703.
Tobacco Institute (1984) New national survey of smoking and productivity in the workplace, *Tobacco Observer* **9**, 6–7.
Trichopoulos, D., Kalandidi, A., and Sparros, L. (1983) Lung cancer and passive smoking: Conclusion of Greek study, *Lancet* **2**, 677–678.
Trichopoulos, D., Kalandidi, A., Sparros, L., and MacMahon, B. (1981) Lung cancer and passive smoking, *Int. J. Cancer* **27**, 1–4.
U.S. Department of Commerce (1980) Statistical abstracts of the United States: Table 653, Labor force participation rates by race, sex, and age: 1960 to 1979. U.S. Dept. of Commerce, Bureau of the Census, Washington, DC.
U.S. Department of Health and Human Services (1983) Advance report of final mortality statistics 1980, in Monthly Vital Statistics Report, vol. 32. U.S. Department of Health and Human Services, National Center for Health Statistics, Washington, DC.
U.S. Department of Health and Human Services (1981) State legislation on smoking and health 1980. U.S. Dept. of Health and Human Services, Public Health Service, Atlanta, GA.
U.S. Department of Health and Human Services (1979) Changes in cigarette smoking and current smoking practices among adults.

2023381932

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United States, 1978. Advance Data No. 52, U.S. Dept. of Health and Human Services, Washington, DC.
U.S. Department of Health, Education and Welfare (1975) Vital statistics of the United States, life tables, 1974. U.S. Dept. of Health and Welfare, National Center for Health Statistics. Washington, DC.
U.S. Environmental Protection Agency (1984) Carcinogen assessment of coke oven emissions. Final Report EPA 600/6-82 003F, U.S. Environmental Protection Agency, Washington, DC.
U.S. Environmental Protection Agency (1983a) Health assessment document for acrylonitrile. EPA 600/8-82-007 F, pp. 13-178, U.S. Environmental Protection Agency, Washington, DC.
U.S. Environmental Protection Agency (1983b) Radionuclides, background information document. Report EPA/520/1-83-001, U.S. Environmental Protection Agency, Washington, DC.
U.S. Environmental Protection Agency (1982) Coke oven emissions, background information document. U.S. Environmental Protection Agency, Washington, DC.
U.S. Environmental Protection Agency (1980) Final risk assessment on arsenic. U.S. Environmental Protection Agency, Washington, DC.
U.S. Environmental Protection Agency (1979) National emission standards for identifying, assessing, and regulating airborne substances posing a risk of cancer, *Fed. Reg.* 44, 58642-58661.
U.S. Environmental Protection Agency (1979) Final risk assessment on benzene. U.S. Environmental Protection Agency, Washington, DC.
U.S. Environmental Protection Agency (1975) National emission standards for hazardous air pollutants: Proposed standard for vinyl chloride, *Fed. Reg.* 40, 59532.
U.S. Federal Trade Commission (1984) Report of tar, nicotine and carbon monoxide of the smoke of 187 varieties of cigarettes. USFTC, Washington, DC.
U.S. Public Health Service (in press) Lung cancer mortality rates for 1980. U.S. Public Health Service, Division of Health Interview Statistics, Washington, DC.
U.S. Surgeon General (1982) The health consequences of smoking: Smoking and cancer. DHHS Pub. No. 82-50179, U.S. Dept. of Health and Human Services, Washington, DC.
U.S. Surgeon General (1979) Smoking and health. DHEW Pub. No. (PHS) 79-50066. U.S. Dept. of Health, Education, and Welfare.
Wald, N. J., *et al.* (1984a) Urinary cotinine as marker of breathing other people's tobacco smoke, *Lancet* 1, 230-231.
Wald, N. J. and Ritchie, C. (1984b) Validation of studies on lung cancer in nonsmokers married to smokers, *Lancet* 1, 1067.
Wald, N. J. (1978) Smoking as a cause of disease in *Recent Advances in Community Medicine*, A. E. Bennett, ed., vol. I, Churchill Livingstone, Edinburgh.
White, J. R. and Froeb, H. F. (1980) Small airways dysfunction in nonsmokers chronically exposed to tobacco smoke, *New Engl and J. Med.* 302, 720-723.
World Health Organization (1979) Health aspects related to indoor air quality. Euro Reports and Studies no. 21, Regional Office for Europe, Copenhagen, Denmark.
Wynder, E. L. and Goodman, M. T. (1983) Smoking and lung cancer: Some unresolved Issues, *Epidemiol. Rev.* 5, 177-206.
Wynder, E. L. and Hoffman, D. (1967) *Tobacco and Tobacco Smoke – Studies in Experimental Carcinogens*, p. 730. Academic Press, New York.

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NONSMOKER LUNG CANCER RISKS FROM TOBACCO SMOKE EXPOSURE: AN EVALUATION OF REPACE AND LOWREY'S PHENOMENOLOGICAL MODEL

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Contents: I. Introduction; II. The Phenomenological Model; III. Problems with the Phenomenological Model; IV. Is there Independent Support for the Phenomenological Model?; V. Discussion and Conclusions

INTRODUCTION

Nonsmokers may be exposed to measurable amounts of tobacco smoke in indoor environments such as offices; public areas such as shopping centers, bars and restaurants; and private residences, particularly if the ventilation is poor. This passive exposure to environmental tobacco smoke (ETS) is of concern because several epidemiological studies have indicated that ETS exposure may increase the risk of lung cancer (1,2). The magnitude of a possible excess lung cancer risk for nonsmokers from ETS exposure is therefore of interest.

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Repace and Lowrey (3) develop a "phenomenological model" which estimates an annual excess risk from ETS exposure of 7.4 lung cancer deaths (LCD)/100,000 nonsmokers 35 years of age and over. The risk calculation is limited to individuals 35 years of age and over because only 0.26% of lung cancer deaths in 1980 occurred among individuals less than 35 years of age (4). This excess risk, applied to an estimated U.S. population of 62.4 million nonsmokers, 35 years of age and over, predicts 4,655 nonsmoker lung cancer deaths from ETS exposure. The category "nonsmoker" includes both ex-smokers and life-long never smokers.

Repace and Lowrey's phenomenological estimate of the lung cancer risk from ETS exposure has been widely accepted in the U.S. and Canada (5). Yet, the estimate is based on several unrealistic assumptions and on unstable data that warrant closer examination. It is the purpose of this review to examine several problems with the phenomenological model and to evaluate the reliability of the lung cancer risk estimates derived from it.

THE PHENOMENOLOGICAL MODEL

Repace and Lowrey's phenomenological model extrapolates from the observed (hence phenomenological) results of a study on a special group of never smokers to the entire U.S. population of nonsmokers. The calculations use lung cancer incidence data from a cohort study by Phillips et al (6,7) of California Seventh Day Adventist (SDA) never smokers and a second cohort of California never smokers. The SDA cohort of never smokers were followed prospectively from 1960 until mid-1972 and the comparison never smoker cohort, from the American Cancer Society (ACS) 25-state study, was followed from 1960 to the end of 1976.

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The study by Phillips et al does not examine the association between ETS exposure and lung cancer, nor is any information obtained on ETS exposure. However, the SDA group was probably less exposed to ETS than the nonSDA group because less than two percent of the SDAs were self-reported smokers as a result of the church proscription against smoking. Consequently, SDA never smokers are not likely to be exposed to ETS in church operated businesses, in their own homes, or in the homes of other church members.

Table I gives, for both SDA and nonSDA never smokers, the observed number of lung cancer deaths and the lung cancer death rate per 100,000 person-years for each 5-year age group starting from age 35. The age standardized relative risk of lung cancer for the SDA men and women compared to the nonSDA men and women is 1.73 and 2.54, respectively.

Repace and Lowrey assume that *all* of the difference in the lung cancer risk between SDA and nonSDA never smokers is caused by a difference in exposure to ETS. They estimate the lung cancer risk from ETS exposure in the following manner. First, the age-specific lung cancer risks for SDA never smokers are subtracted from the comparable risks for nonSDA never smokers. For example, the lung cancer death rate for nonSDA never smoking women 85 years of age and over is 126.73 per 100,000 (Table I, column 5), while the rate for the comparable group of SDA women is 22.54 (Table I, column 3). The difference, 104.19 LCD/100,000, is attributed entirely to ETS exposure. Second, the age-specific differences in risk for men and women are weighted in order to derive a single age-specific risk estimate. For example, the difference between SDA and nonSDA men over 85 is 48.96 LCD/100,000. The combined average for the over 85 age group, weighted by the number of person-years of observation for

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TABLE I

Number of lung cancer deaths and the lung cancer death rate per 100,000 person-years (LCD/100,000) for Seventh Day Adventist (SDA) and nonSDA never smokers (1)

MEN	SDA		nonSDA	
Age	# Deaths*	LCD/100,000	# Deaths*	LCD/100,000
35-39	0	0	0	0
40-44	0	0	0	0
45-49	0	0	0	0
50-54	0	0	1	5.18
55-59	1	10.80	2	8.39
60-64	1	11.44	4	20.48
65-69	4	46.04	8	56.72
70-74	1	17.53	0	0
75-79	0	0	2	30.58
80-84	1	28.89	4	113.73
85+	2	70.73	2	119.69

WOMEN	SDA		nonSDA	
Age	# Deaths*	LCD/100,000	# Deaths*	LCD/100,000
35-39	0	0	0	0
40-44	0	0	1	6.07
45-49	0	0	2	5.22
50-54	1	4.51	4	6.49
55-59	1	4.05	8	11.22
60-64	1	4.58	7	10.76
65-69	1	4.92	4	7.19
70-74	0	0	9	20.34
75-79	1	5.32	10	34.19
80-84	8	57.87	6	39.21
85+	2	22.54	10	126.73

*The actual number of observed deaths is estimated from Repace and Lowrey's figures, which were adjusted for the effect of outmigration.

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men and women, is 92.6 LCD/100,000. Third, the average risk estimates for both sexes combined are applied to the estimated population distribution of the 62.4 million nonsmokers 35 years of age and over in the U.S. in 1980, which is assumed to be the same as the age distribution of the entire U.S. population in 1974. For example, the excess lung cancer risk from ETS exposure of 92.6 LCD/100,000 men and women 85 years of age and over, combined, is applied to the estimated 981,164 nonsmokers over 85 in the U.S. in 1980. This predicts 909 excess lung cancer deaths in this age group [(92.6 x 981,164)/100,000]. Fourth, the excess lung cancer deaths for all age groups over 35 are summed. This adds up to 4,655 excess lung cancer deaths among the 62.4 million nonsmokers, which gives an annual risk from ETS exposure of 7.4 LCD/100,000 nonsmokers 35 years of age and over.

PROBLEMS WITH THE PHENOMENOLOGICAL MODEL

There are three problems with Repace and Lowrey's phenomenological model.

1. The lung cancer risk estimates derived from the SDA study are based on very few observed deaths and are unstable.
2. The apparent differences in lung cancer mortality between SDA and nonSDA never smokers may be due to a variety of factors other than ETS exposure.
3. A number of assumptions and calculations are made that are clearly incorrect.

1. Stability of the Model

The reliability of Repace and Lowrey's phenomenological model is strongly dependent upon the accuracy of the

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age-specific lung cancer death rates calculated for the SDA and nonSDA never smokers. However, the SDA lung cancer death rates, in particular, are not likely to be accurate because they are based on a small number of observed lung cancer deaths.

There were only 10 lung cancer deaths among the SDA men (the difference in risk between SDA and nonSDA men is not, in fact, statistically significant) and 15 deaths among the SDA women (6). The age-specific risks for 9 out of the 22 age groups are based on only one lung cancer death and there were no lung cancer deaths in an additional nine of the age groups. Consequently, the age-specific rates for SDA men and women varied widely, as shown in column 3 of Table I. For example, the lung cancer death rate for SDA women over 85 was less than half the rate for the preceding age group. This decline of lung cancer risk with age must be due to random or other errors, because lung cancer death rates invariably increase with age (8,9).

The small number of lung cancer deaths observed for the SDA cohort may be partly attributable to a lack of histopathological verification and incomplete follow-up. These two problems did not occur in the nonSDA cohort, which may partly explain the large difference in the lung cancer rates between the two cohorts. The SDA cohort was also relatively small so that few lung cancer deaths would be expected. Random fluctuations in the number of observed lung cancer deaths would result in large differences in the age-specific lung cancer death rates. Therefore, these rates are very unstable.

The phenomenological model is very sensitive to errors in the estimated lung cancer death rates for SDA never smokers. For example, adding one lung cancer death to the 70-74 year age

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group for SDA women results in 183 fewer estimated deaths per year in the U.S., according to the method used by Repace and Lowrey (3). A second example concerns the over 85 age group. As noted above, the observed lung cancer death rate of 22.5 LCD/100,000 SDA women 85 years of age and older is not likely to be correct, and is probably a large underestimate of the true rate. This underestimate is responsible for a significant proportion of all lung cancer deaths attributed to ETS exposure. 909, or 19.5%, of the estimated 4,655 excess lung cancer deaths in the U.S. among all nonsmokers 35 years of age and over occur among individuals over 85 years of age. The majority of these deaths are attributable to the estimated risk for women over 85 because of the large difference of 104.2 LCD/100,000 between the rate of 22.5 LCD/100,000 SDA women and 126.7 LCD/100,000 nonSDA women in this age group. An increase in the lung cancer death rate for SDA women over 85 years of age to a rate greater than that observed for women between 80-84 years of age (57.9 LCD/100,000) would decrease the difference between the SDA and nonSDA cohorts and consequently decrease the predicted risk and number of deaths attributable to ETS exposure.

For several age groups, the phenomenological model predicts more lung cancer deaths among never smokers as a result of exposure to ETS alone than a reasonable estimate of the total number of lung cancer deaths from all causes, as shown in Table II for men and Table III for women. The number of expected lung cancer deaths is obtained by multiplying the age-specific lung cancer death rates from ETS exposure alone (column 3) or from all causes (column 5) by an estimate of the number of never smokers in each age and sex category (column 2). The latter is obtained by combining the 1979/1980 Health Interview Survey

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TABLE II

Comparison of the estimated number of lung cancer deaths (LCD) in 1980 among male never smokers from exposure to environmental tobacco smoke (ETS) and from all causes

		ETS EXPOSURE		ALL CAUSES	
Age	Never-smoking Population*	LCD/100,000**	Estimated Deaths†	LCD/100,000††	Estimated Deaths†
35-39	1,993,771	0	0	0	0
40-44	1,713,901	0	0	7.6667	131.3986
45-49	1,239,080	0	0	3.0333	37.5690
50-54	1,328,782	5.1779	68.80		
55-59	1,127,890	-2.4152	-27.24	10.1333	114.2884
60-64	1,162,938	9.0651	105.38	17.2667	200.7314
65-69	1,084,361	10.6740	116.81	27.4333	300.2193
70-74	886,253	-17.9301	-159.38	77.9000	690.3811
75-79	722,398	30.5764	220.88	44.2667	319.7818
80-84	382,727	84.8475	324.73	68.6667	263.5719
85+	303,790	48.9412	148.74	94.8000	287.9928
			Total 802.74		Total 2,447.38

* Estimated from the 1979/1980 HIS distribution of never smokers of all races and the U.S. Census (10) estimate of the population size in 1980.
** From Table C1, column 9, Repace and Lowrey (3). Each age-specific rate is the LCD/100,000 nonSDA never smokers per year minus the rate for the SDA never smokers.
†Equals the relevant LCD/100,000 times the never smoking population divided by 100,000.
†† Average lung cancer death rates per year for 1960-1972 for the ACS population of never smokers (8).

TABLE III

Comparison of the estimated number of lung cancer deaths (LCD) among female never smokers from exposure to environmental tobacco smoke (ETS) and from all causes

		ETS EXPOSURE		ALL CAUSES	
Age	Never-smoking Population*	LCD/100,000**	Estimated Deaths†	LCD/100,000††	Estimated Deaths†
35-39	3,388,446	0	0	0	0
40-44	2,870,212	6.0731	174.31	2.3333	66.97
45-49	2,887,920	5.2193	150.71	3.6000	103.96
50-54	3,243,330	1.9903	64.21	5.3000	171.84
55-59	3,147,137	7.1737	225.77	7.0667	222.40
60-64	2,982,713	6.1623	184.40	13.6000	405.65
65-69	2,979,828	2.2710	67.67	16.1667	481.74
70-74	2,616,364	20.3400	532.17	20.8333	545.06
75-79	2,157,707	28.8750	623.04	34.7000	748.72
80-84	1,528,857	-16.6560	-255.22	45.8000	700.22
85+	1,026,930	104.1890	1,069.93	92.4667	936.80
			Total 2607.01		Total 3,985.37

* Estimated from the 1979/1980 HIS distribution of never smokers of all races and the U.S. Census (10) estimate of the population size in 1980.
** From Table C1, column 9, Repace and Lowrey (3). Each age-specific rate is the LCD/100,000 nonSDA never smokers per year minus the rate for the SDA never smokers.
†Equals the relevant LCD/100,000 times the never smoking population divided by 100,000.
†† Average lung cancer death rates per year for 1960-1972 for the ACS population of never smokers (8).

(HIS) estimates of the proportion and age and sex distribution of never smokers with the U.S. Census estimate of the population 35 years of age and over in 1980 (10,11). The estimated number of lung cancer deaths from ETS exposure alone is given in column 4 of each table. The all causes estimate uses the lung cancer death rates observed for never smokers in the ACS 25-state study (8). The estimated number of lung cancer deaths from all causes is given in column 6 of each table.

The phenomenological model estimates fewer male never smoker lung cancer deaths from ETS exposure than the estimated number of deaths from all causes. However, for women, the model estimates almost the same number of lung cancer deaths from ETS exposure than from all causes for the age group 70-74 and more deaths from ETS exposure than from all causes for the age groups 40-44, 45-49, 55-59 and 85+. For example, the estimate of 1,069 female deaths attributable to ETS exposure in the 85+ group is almost twice the estimate of 539 deaths from all causes. The fact that the phenomenological model predicts, for several age groups, more lung cancer deaths from ETS exposure alone than from all causes indicates that the death rates used in the model are unreliable indicators of the real risk associated with ETS exposure.

2. Other Causes for the Difference in Risk Between SDA and NonSDA Nonsmokers

Repace and Lowrey's phenomenological model assumes that all of the difference in lung cancer incidence between the SDA and nonSDA never smokers is caused by ETS exposure. This assumption does not allow for other possible confounding factors, such as

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differences between the SDA and nonSDA cohorts in diet or exposure to occupational carcinogens.

The possibility of confounding by occupation, though possible, cannot be assessed. Phillips et al (6,7) did not determine the occupational distribution of SDA and nonSDA never smokers because occupation was coded differently for the two groups. Occupation would affect the estimated risks if a higher proportion of the nonSDA versus SDA never smokers were blue-collar workers exposed to carcinogens at work.

Confounding by diet is probable. A low rate of consumption of vegetables or foods containing retinoids has been linked to an increased lung cancer risk (12-15). The SDAs are known to follow a lacto-ovo vegetarian diet and this may reduce their risk for many types of cancer, both through a decreased intake of fats and an increased consumption of vegetables, eggs, and milk high in retinoids or vitamin A. Therefore, the low lung cancer incidence among the SDA never smokers may be due to dietary factors such as an above average consumption of retinoids. A possible dietary cause for the difference in the lung cancer risk between the SDA and nonSDA never smokers is supported by the lower risks for colon-rectal and breast cancer observed for the SDA group. Several studies have found that diet may be a risk factor for colon-rectal (16) and breast cancer (17). There was a statistically significant decrease in the relative risk (RR) of breast cancer (RR = 0.81) and colon-rectal cancer (RR = 0.56) for SDA women never smokers compared to the nonSDA women never smokers (6). The relative risk of colon-rectal cancer for SDA men was also below 1.0 but was not statistically significant.

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3. Other Errors

There are three instances where Repace and Lowrey make inappropriate assumptions.

1. Repace and Lowrey incorrectly assume that nonsmokers have the same sex and age distribution as the entire U.S. white population. A comparison between the 1979/1980 HIS data and U.S. Census data (10) shows that the age distribution of the U.S. nonsmoking population is skewed towards the older age classes, as shown in Table IV. For example, 25.38% of male nonsmokers 35 years of age and over are between the ages of 35 and 44 compared to 28.76% of all U.S. males 35 years of age and over and 10.5% of nonsmoking males are 75 years of age or over compared to 8.1% of all U.S. males.
2. Repace and Lowrey combine both sexes, instead of calculating the expected number of deaths for each sex separately. The latter is required, as the age distribution of female never and nonsmokers is different from the comparable distributions for men, as shown in Table IV.
3. Repace and Lowrey estimate the excess lung cancer deaths from ETS exposure for nonsmokers (ex- and never smokers combined). This should not be done because the difference in lung cancer death rates between the SDA and nonSDA group is for *never* smokers only. The excess risk for ex-smokers from exposure to ETS may differ from the risk for never smokers, either because of their previous smoking habit or because ever smokers are more likely than never smokers to be exposed to carcinogens at work (18).

IS THERE INDEPENDENT SUPPORT FOR THE PHENOMENOLOGICAL MODEL?

The phenomenological model, based on only 25 lung cancer deaths among never smoking men and women SDAs combined, provides

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TABLE IV

1979/1980 HIS estimates of the age distributions of never and nonsmokers and the U.S. Census estimate for adults 35 years of age and over

MEN

	HIS		U.S. Census
Age	Never	Nonsmoker	All
35-44	31.00	25.38	28.76
45-54	21.47	23.01	24.80
55-64	19.15	22.40	23.00
65-74	16.56	18.66	15.34
75-84	9.24	8.44	6.54
85+	2.54	2.06	1.56

WOMEN

	HIS		U.S. Census
Age	Never	Nonsmoker	All
35-44	21.70	23.09	25.38
45-54	21.25	21.67	22.67
55-64	21.25	21.92	22.34
65-74	19.40	19.21	17.10
75-84	12.78	11.14	9.46
85+	3.56	2.82	3.05

an unstable estimate of the lung cancer risk for nonsmokers as a result of ETS exposure. Repace and Lowrey, though not directly addressing this problem, use corroborative evidence to defend the estimated annual risk of 7.4 LCD/100,000. They argue that their findings are supported by 1) the results of a linear extrapolation model, after adjusting for the nonsmoker's retained ETS dose and 2) a sensitivity analysis of the ACS study on ETS exposure and lung cancer (8).

1. Linear Extrapolation Model

Nonsmoker lung cancer risks from ETS exposure can be calculated by using a linear extrapolation model. This method

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estimates the risk for nonsmokers by dividing the lung cancer risk for current smokers by the ratio between the smoker's and nonsmoker's average exposure. The linear model requires estimates of several parameters such as the number of nonsmokers and current smokers in the U.S. and their average daily exposure to ETS. The linear extrapolation model also requires three assumptions, 1) that it is valid to derive the lung cancer risk for nonsmokers exposed to ambient ETS from the observed risk for smokers exposed to directly inhaled tobacco smoke, 2) that there is a linear relationship between risk and each unit of exposure, and 3) that no threshold exists at very low exposures where the risk falls to zero.

Repace and Lowrey (3) pioneered the development of the linear model for estimating nonsmoker lung cancer risks from ETS exposure. Their linear extrapolation calculation estimates a lung cancer risk for nonsmokers of 0.83 LCD/100,000 from ETS exposure. This is significantly lower than the phenomenological model's estimate of 7.4 LCD/100,000. Repace and Lowrey argue that the difference between the two risk estimates can be explained by the difference between the nonsmoker's inhaled exposure and the equilibrium ETS dose.

The inhaled exposure is based on the amount of ETS inhaled, whereas the equilibrium dose calculates the steady-state burden of particulate ETS in the lungs from the inhaled exposure. The following equation calculates the equilibrium dose (3):

$$\text{Equilibrium dose} = Dn\delta\tau,$$

where Dn equals the inhaled exposure in milligrams (mg); δ equals the deposition fraction for tobacco smoke particulates in the lungs; and τ equals the mean life for pulmonary clearance,

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which is assumed to be 101 days. The deposition fraction for nonsmokers has been empirically estimated to be approximately 11% (19). Repace and Lowrey estimate that the equilibrium dose for the average nonsmoker inhaling 1.43 mg/day is 16 mg/day (1.43 mg x .11 x 101), which is 1/34th of their estimate of the average smoker's daily inhaled exposure of 544 mg. Repace and Lowrey's estimate of the lung cancer risk for current smokers is 315.6 LCD/100,000. Therefore, the linear model predicts a lung cancer risk for never smokers of 9.28 LCD/100,000 (315.6/34). Accordingly, the risk estimates derived from the linear and phenomenological models are approximately the same, with the phenomenological model providing the lower risk estimate.

In fact, Repace and Lowrey's adjustment of the linear model is based on an incorrect comparison between two completely different estimates of exposure. The *exposure* of smokers is compared to the *equilibrium dose* of nonsmokers. Obviously, the correct comparison is either between the smoker and nonsmoker's inhaled exposure or between the smoker and nonsmoker's equilibrium dose. An estimate of the lung cancer risk for nonsmokers, using the linear model and the equilibrium dose, can be determined using an estimate of the deposition fraction for smokers.

The deposition fraction for smokers has been empirically estimated to be between 70% and 96% (19-22). We will assume an average retention rate of 80% for smokers. The equilibrium dose for smokers, using Repace and Lowrey's estimate of the inhaled exposure for smokers of 544 mg, is 43,955 mg (544 x 0.80 x 101). Therefore, nonsmokers have only 1/2,747th of the smoker's equilibrium dose (43,955/16) and, consequently, only 1/2,747th of the smoker's lung cancer rate, or 0.11 LCD/100,000

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(315.6/2,747). Instead of supporting the phenomenological estimate, the use of the equilibrium dose in the linear model significantly decreases the likelihood that the phenomenological model provides a reliable estimate of the average risk for nonsmokers from ETS exposure.

2. Sensitivity Analysis

Repace and Lowrey (3) conduct a sensitivity analysis to explain the difference in the results of two cohort studies, one in Japan and one in the U.S., of female nonsmokers married to smokers. The sensitivity analysis uses an estimate of risk per 1 mg of exposure to tobacco smoke particulate that is based on the phenomenological model. Garfinkel's (8) analysis of the ACS data for 176,731 American women followed from 1960 until 1971 finds a statistically nonsignificant increased relative risk of 1.20 for never smoking women married to smokers. Conversely, Hirayama's (23) study of 91,540 Japanese women followed from 1966 to 1981 finds a statistically significant increased relative risk of 1.78, which is closer to the relative risk of 1.73 for men and 2.54 for women on which the phenomenological model is based.

Repace and Lowrey suggest that the ACS relative risk is unrealistically low and actually results from confounding with workplace exposure, which they estimate to contribute four times as much exposure to ETS as the home environment. The ACS study does not include workplace exposure as a factor in deciding exposure status. Nonsmoking women married to smokers are defined as exposed, whereas nonsmoking women married to nonsmokers are defined as unexposed. Repace and Lowrey estimate that 38 percent

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of the original unexposed and exposed ACS women worked outside the home and were therefore exposed to ETS at work.

Repace and Lowrey's sensitivity analysis recalculates the ACS results using an estimate of the lung cancer risk per 1 mg of ETS exposure and an estimate of the amount of home and workplace exposure recieved by the original ACS exposed and unexposed cohorts. The lung cancer risk per 1 mg of exposure is estimated by combining the phenomenological model's estimated risk of 7.4 LCD/100,000 with an estimated average daily exposure to 1.43 mg of ETS. This estimates a risk of 5 LCD/100,000 per mg of exposure. The excess lung cancer risk from ETS exposure for each of four exposure categories - women not exposed at home or at work, women exposed at work only, women exposed at home only, and women exposed at home and at work - is determined by multiplying the estimated exposure by the risk of 5 LCD/100,000 per mg of exposure. For example, Repace and Lowrey estimate that employed women are exposed to 1.82 mg/day and women who live with a smoker are exposed to 0.45 mg/day. Therefore, women who both work and live with a smoker are exposed to 2.27 mg/day for an excess risk of 11.35 LCD/100,000 (2.27 x 5). The excess risk from ETS exposure is added to the background lung cancer risk in the absence of any exposure in order to construct an expected death rate for each of the four exposure categories. The lung cancer death rate of 8.7 per 100,000 person-years found in the Japanese cohort study for nonsmoking women married to nonsmoking men is used as the base lung cancer rate in the absence of either work or home exposure to ETS.

The relative risk of 1.19 for women who live with a smoker versus those who do not, determined after the adjustment for work exposure and the use of the phenomenological model's

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estimate of risk, is only marginally different from the original "unadjusted" risk of 1.20. According to Repace and Lowrey, this indicates that the estimated risk from the phenomenological model is a good estimator of the true risk in this cohort study.

Problems with the sensitivity analysis

Repace and Lowrey's sensitivity analysis is dependent upon 1) the applicability of the background lung cancer death rate in the absence of smoking and 2) the relative importance of exposure at work versus exposure at home.

1. The background risk

The use of the risk of 8.7 LCD/100,000 Japanese women nonsmokers as an estimate of the background risk in the Garfinkel study is inappropriate. Repace and Lowrey note that the risk of 8.7/100,000 is an 'age-adjusted' risk, *but it is adjusted to the age distribution of the husbands of the Japanese female nonsmokers and not to the ACS women at risk.* It is unlikely that the age distribution of Japanese male nonsmokers is the same as the age distribution of American female nonsmokers.

The age distribution of the entire ACS population of nonsmoking women is available and can be compared against the age distribution used in Hirayama's study. Both distributions are given in Table V. If we assume that the age distribution of nonsmoking women married to nonsmokers in the ACS study is similar to the age distribution of all nonsmoking ACS women, it is possible to apply the age-specific lung cancer death rates from the Japanese study to the ACS population distribution, as shown in Table VI. The background lung cancer death rate is

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TABLE V

Age distribution of 375,381 nonsmoking women at the start of the ACS study and the nonsmoking husbands of 21,895 nonsmoking women at the start of the Hirayama study

AGE	ACS (24)	Hirayama (1)
under 49*	0.3374	0.2845
50-59	0.3278	0.3558
60-69	0.2201	0.3252
70+	0.1147	0.0345

* ACS population starts at 30 years of age and the Hirayama population of husbands at 40 years of age.

TABLE VI

Estimated lung cancer death rate (LCD/100,000) for nonsmoking women from the ACS study (8) after using the husband-age-specific risks for nonsmoking women from Hirayama (1)

AGE	Hirayama: LCD/100,000*	Age Distribution of ACS nonsmokers	Expected LCD's
under 49	4.01	0.3374	1.35
50-59	8.02	0.3278	2.63
60-69	15.80	0.2201	3.48
70+	41.39	0.1147	4.75
		Total LCD/100,000	12.21

* Age-specific LCD/100,000 person years, adjusted for the husband's age (1).

subsequently increased from 8.7 to 12.21 LCD/100,000. This is similar to the rate for all nonsmoking ACS women of approximately 13/100,000, which indicates that there is no increase in risk in the ACS study from ETS exposure.

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The background risk of 12.21 LCD/100,000 can be used in the sensitivity model, keeping in mind that the model is extremely insensitive to large differences in risk. For example, the use of the phenomenological estimate of the excess lung cancer risk from ETS exposure results in a 1% difference between the adjusted relative risk of 1.19 and the observed relative risk of 1.20. Decreasing the estimate of the excess risk 8.3-fold only increases the difference between the adjusted and observed relative risks by 17%. A change in the background risk from 8.7 LCD/100,000 to 12.21 LCD/100,000 increases the difference between the adjusted and observed relative risk from 1.0% to 4.6%, which is a significant change considering the insensitivity of the sensitivity analysis. This indicates that the estimate of risk from the phenomenological model is a poor indicator of the true risk in the ACS population.

The use of the background lung cancer rate from the Japanese study is also questionable. It assumes that none of the Japanese women worked. Accordingly, it is unnecessary to adjust their baseline lung cancer death rate for workplace exposure to ETS. In fact, between 31% and 34% of Japanese women worked in paid employment during the time period of the Hirayama study (25), and 15% of Japanese women smoked (26). Therefore, some workplace exposure must have occurred from exposure to the tobacco smoke of fellow male and female employees.

2 Adjustment for work exposure

The sensitivity analysis is dependent upon Repace and Lowrey's estimate, based on an exposure model, that workplace exposure accounts for 80.4% of the total daily average exposure to ETS, while home exposure accounts for only 19.6%. However, there is no independent supporting evidence for Repace and

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Lowrey's estimate on the relative importance of workplace versus home exposure from interview data (27) or from epidemiological studies. None of the four epidemiological studies which specifically examine the effect of exposure of women to ETS at work finds a statistically significant increase in risk (15,28-30).

DISCUSSION AND CONCLUSIONS

Other than Repace and Lowrey's phenomenological model, two methods are available for estimating the lung cancer risk or number of lung cancer deaths among nonsmokers from ETS exposure. These methods consist of 1) a downward extrapolation from the risk for smokers and 2) the population attributable risk (PAR) equation (31).

The linear extrapolation model was developed by Repace and Lowrey (3) and has been further refined by Arundel et al (32). As shown above, Repace and Lowrey's linear model does not support the results of the phenomenological model. In addition, the risk estimate of 0.83 LCD/100,000 nonsmokers, determined by Repace and Lowrey from the linear model, is inaccurate. This is because their linear model overestimates the average nonsmoker's exposure to ETS and the average current smoker's lung cancer risk. For example, the latter is estimated by Repace and Lowrey after assuming that all lung cancer deaths among ever smokers (ex- and current combined) occur only among current smokers. This results in a significant overestimate of the lung cancer risk for current smokers and, subsequently, for never smokers.

The linear model developed by Arundel et al (32) estimates a lung cancer risk from ETS exposure for both sexes combined of 0.022 LCD/100,000. This estimate is based on the equilibrium

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dose. However, the calculations by Arundel et al, as do those by Repace and Lowrey, rest on several assumptions that may not be tenable.

The large difference in the linear estimates by Repace and Lowrey and by Arundel et al illustrates the extensive uncertainty which accompanies the results of these types of models. Large errors in the risk estimates are possible in any type of model. Arundel et al provide a "sensitivity calculation" which indicates the effect of a 1% change in each parameter of the linear model on the final risk estimate. This is useful for determining the most important parameters in the model, but does not replace scientifically desirable confidence limits.

The PAR equation estimates the number of lung cancer deaths from ETS exposure using differences in risk observed in epidemiological studies. In this respect it is similar to the phenomenological model, but the number of lung cancer deaths from ETS exposure is calculated using only three parameters: the exposure rate in the population of interest, the relative risk of exposure, and an estimate of the number of nonsmokers in 1980 (obtainable from the 1979/1980 HIS). Therefore, the PAR equation appears to be a remarkably simple method for estimating the number of lung cancer deaths among nonsmokers from ETS exposure. However, neither the exposure rate nor the relative risk are known for the entire population of nonsmokers. The exposure rate could be estimated from HIS data on the employment status of nonsmokers and the proportion who live with a smoker. Unfortunately, the relative risk cannot be estimated because most of the epidemiological studies on this problem only calculate risks for a subset of all nonsmokers (married women) exposed to a subset of all possible exposures (spouse's smoke) (2,8,23,33-37).

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The relative risk is particularly difficult to obtain because the PAR method requires an estimate of the relative risk for the *average* regularly exposed nonsmoker compared to the *average* unexposed nonsmoker. The relative risk must not be determined from a subset of the regularly exposed population of nonsmokers. Exposure should also be defined as cumulative exposure to all sources of ETS.

An accurate method for estimating the lung cancer risk and the number of lung cancer deaths among nonsmokers from ETS exposure is of considerable interest. Repace and Lowrey's phenomenological estimate of the lung cancer risk for nonsmokers from ETS exposure is unstable and inaccurate. The evidence presented by Repace and Lowrey to support the plausibility of their estimate is based on several errors and unrealistic assumptions. Without corroborating data from independent sources, little confidence can be placed in their results.

The results of the linear extrapolation model by Arundel et al and the results of the best available epidemiological studies further indicate that the phenomenological estimate is in error. Both predict an extremely small excess lung cancer risk from ETS exposure. Conversely, Repace and Lowrey argue that the 12 epidemiological studies on ETS exposure support the plausibility of a significant excess risk from ETS exposure. However, with one exception (for men exposed at work) (29), the observed risks are statistically significant only when the analysis of exposure is limited to a comparison between female never smokers who are currently married to smokers versus married to nonsmokers. Exposure may also occur at work or at home from other household members and from previous spouses. Therefore, epidemiological studies should examine cumulative exposures from all sources.

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The best available epidemiological analyses, by Koo et al (28) in Hong Kong and Garfinkel et al (30) in the United States, examine exposure from all sources. Neither find a statistically significant increase in risk. Garfinkel et al (30) also correlate cumulative exposures from all sources over the previous five or twenty-five years against lung cancer incidence and find a negative correlation between an increase in exposure and lung cancer. These analyses of cumulative exposures indicate that an association between lung cancer among nonsmokers and the spouse's smoking habit may be caused by confounding, not by ETS exposure. Confounding could occur either from life-style factors and occupational exposures associated with active smoking or by unreported active smoking by self-reported nonsmokers (38).

REFERENCES

1. Hirayama, T. Prev. Med. 13:680, 1984.
2. Trichopoulos, D., Kalandidi, A. and Sparros, L. Lancet 2:677, 1983.
3. Repace, J.L. and Lowrey, A.H. Environ. Int. 11:3, 1985.
4. National Center for Health Statistics. United States Dept. of Health and Human Services, Public Health Service. Division of Vital Statistics, Statistical Resources Branch, 1986. Data available on request.
5. Marwick, C. JAMA 24/31:2937, 1985.
6. Phillips, R.L., Ruzma, J.W., Beeson, W.L. and Lotz, T. Am. J. Epidemiol. 112:296, 1980.
7. Phillips, R.L., Garfinkel, L., Ruzma, J.W., Beeson, W.L., Lotz, T. and Brin, B. JNCI 65:1097, 1980.
8. Garfinkel, L. JNCI 66:1061, 1981.
9. Enstrom, J.E. and Godley, P.H. JNCI 65:1175, 1980.

2023381947

10. USDC (United States Dept. of Commerce). Bureau of the Census. Preliminary estimates of the population of the United States, by age, sex, and race: 1970 to 1981. Population Estimates and Projections Series P-25, No. 917, 1982.

11. The HIS is an ongoing survey which uses a probability sample of households in the U.S. The 1979/1980 survey contains smoking, age, and sex information for 37,604 individuals 17 years of age and over. Due to the size of the sample, the HIS provides the best available estimate of the proportion of American adults who are never smokers and their age and sex distributions. A computer readable tape of the 1979/1980 HIS data was obtained from the National Center for Health Statistics. All analyses of the HIS were conducted by us.

12. Wynder, E.L. and Goodman, M.T. Epidemiol. Rev. 5:177, 1983.
13. Byers, T., Vena, J., Mettlin, C., Swanson, M. and Graham, S. Am. J. Epidem. 120:769, 1984.
14. Hinds, M.W., Kolonel, L.N., Hanlan, J.H., and Lee, J. Am. J. Epidemiol. 119:227, 1984.
15. Wu, A.H., Henderson, B.E., Pike, M.C. and Yu, M.C. JNCI 74:747, 1985.
16. Graham, S. in Reviews in Cancer Epidemiology edited by A.M. Lilienfeld. Elsevier. Amsterdam, Oxford. 1983.
17. Miller, A.B., Kelly, A., Choi, N.W., Mathews, V., Morgan, R.W., Munan, L., Burch, J.D., Feather, J., Howe, G.R. and Jain, M. Am. J. Epidemiol. 107:499, 1978.
18. Sterling, T. and Weinkam, J. Arch. Environ. Health 33:313, 1978.
19. Hiller, F.C., McKusker, K.T., Mazumber, M.K., Wilson, J.D. and Bone, R.C. Am. Rev. Respir. Dis. 125:406, 1982.
20. Hoegg, U.R. Environ. Health Perspec. Oct:117, 1972.

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

21. Hiller, F.C. Prev. Med. 13:602, 1984.

22. Dalhamn, T. JNCI Mono. 28:79, 1968.

23. Hirayama, T. Br. Med. J. 282:183, 1981.

24. Garfinkel, L. JNCI 65:1169, 1980.

25. JML (Japanese Ministry of Labour). The Status of Wom
Japan Women and Young Workers Bureau, Ministry of L
Tokyo, 1983.

26. Hayashi, T. World Smoking and Health 5:40, 1980.

27. Friedman, G.D., Petitti, D.B. and Baivol, R.D. AJPH
1983.

28. Koo, L.C., Ho, J.H.-C. and Saw, D. J. Exp. Clin. Can.
3:277, 1984.

29. Kabat, G.C. and Wynder, E.L. Cancer 53:1214, 1984.

30. Garfinkel, L., Auerbach, O. and Joubert, L. JNCI 75:46
1985.

31. Cole, P., MacMahon, B. Brit. J. Prev. Med. 25:242, 1971

32. Arundel, A., Irwin, T., Sterling, T. and Wienkam, J.
Submitted for publication. Copy available from the autho
request. 1986.

33. Chan, W.C. and Fung S.C. in Cancer Campaign Vol. 6, Cance
Epidemiology. Gustav Fischer Verlag, Stuttgart.1982.

34. Correa, P., Pickle, L.W., Fontham, E., Lin, Y. and Haenszc
W. Lancet 2:595, 1983.

35. Knoth, A., Bohn, H. and Schmidt, F. Med. Klin. 78:66, 1983.

36. Gillis, C.R., Hole, D.J., Hawthorne, V.M. and Boyle, P.
European. J. Respir. Dis. (Suppl.) 133:121, 1984.

37. Sandler, D.P., Everson, R.B. and Wilcox, A.J. Am. J.
Epidemiol. 121:37, 1985.

38. Lehnert, G. Prev. Med. 13:730, 1984.

2023381948

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NEVER SMOKER LUNG CANCER RISKS FROM EXPOSURE TO PARTICULATE TOBACCO SMOKE

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The average particulate environmental tobacco smoke (ETS) exposure of never and current smokers and the average lung cancer mortality rate for current smokers is estimated from empirical data. These estimates are used in a linear downward extrapolation of the lung cancer risk/mg of particulate ETS exposure for current smokers to calculate the average lung cancer risk for never smokers and the number of never smoker lung cancer deaths (LCD) in the U.S. in 1980 from exposure to particulate ETS. The estimated average daily inhaled particulate ETS exposure for never smokers is 0.62 mg/day for men and 0.28 mg/day for women. The average never smoker is estimated to retain 11% of the inhaled exposure, for a daily retained exposure of 0.07 mg for men and 0.03 mg for women. Other estimates are: a daily retained exposure for current smokers of 310 mg for men and 249 mg for women, a smoking-attributable lung cancer risk for current smokers in 1980 of 284 LCD/100,000 men and 121 LCD/100,000 women, and an annual retained-exposure lung cancer risk for never smokers of 0.64 LCD/100,000 men and 0.015 LCD/100,000 women. These risks and exposures estimate 12 lung cancer deaths among never smokers from exposure to particulate ETS: 8 among the 11.96 million male never smokers and 4 among the 28.85 million female never smokers in the U.S. in 1980. Conversely, between 655 and 3,610 never smoker lung cancer deaths are estimated from methods based on the average lung cancer risk observed in epidemiological studies of exposure to ETS. Three possible reasons for the discrepancy between the exposure and risk-based estimates are discussed: the excess risks observed in epidemiological studies are due to bias, the relationship between exposure and risk is supralinear, or sidestream tobacco smoke is substantially more carcinogenic than an equivalent exposure to mainstream smoke.

Introduction

Never smokers can be passively exposed to tobacco smoke at work, at home, and in public areas such as shopping centers and restaurants, particularly if the ventilation is poor. Concern over the average never smoker's lung cancer risk from exposure to "environmental" tobacco smoke (ETS) has grown considerably since a 1981 study reported an association between lung cancer in nonsmokers and marriage to a smoker (Hirayama, 1981). Since then, other epidemiological studies of the association between lung cancer among nonsmokers and ETS exposure from living with a smoker have been conducted in Japan (Akiba *et al.*, 1986), Greece (Trichopoulos *et al.*, 1983), Hong Kong (Chan & Fung, 1982; Koo *et al.*, 1985), Sweden (Pershagen *et al.*, 1987), Great Britain (Gillis *et al.*, 1984; Lee *et al.*, 1986), and the U.S. (Garfinkel *et al.*, 1981; Correa *et al.*, 1983; Buffler *et al.*, 1984; Kabat & Wynder, 1984; Garfinkel *et al.*, 1985; Dalager *et al.*, 1986; Brownson *et al.*, 1987; and Humble *et al.*, 1987). The results of these studies have been used to estimate an average excess lung cancer risk for never smokers of 30% from ETS exposure (Blot & Fraumeni, 1986; NRC, 1986; Wald *et al.*, 1986; Wigle *et al.*, 1987). Alternatively, the risk can be estimated by downward extrapolation techniques based on the lung cancer risk for current smokers and the average exposure of current and never smokers. The former method is a risk-based estimate whereas the latter is an exposure-based estimate.

Linear Extrapolation

This study uses linear downward extrapolation to estimate the lung cancer risk and the number of U.S. lung cancer deaths for male and female never smokers in 1980 from exposure to ETS. The final estimate of the number of ETS-attributable never smoker lung cancer deaths requires four preliminary estimates:

1. The number of never smokers at risk,
2. The average tobacco smoke exposure of never smokers,

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3. The average tobacco smoke exposure of current smokers, and
4. The smoking-attributable lung cancer risk for current smokers.

The lung cancer risk for never smokers is estimated by dividing the lung cancer risk for active smokers by the ratio of the average tobacco smoke exposure of smokers and never smokers. The estimated lung cancer risk for never smokers is then used to predict the number of ETS-attributable never smoker lung cancer deaths in the U.S. in 1980. This is done by multiplying the estimated lung cancer risk for each sex by an estimate of the total U.S. population of never smokers of each sex ≥ 35 years of age. Appendix A lists the equations and parameters used in the linear extrapolation estimate.

Estimating the smoker/never smoker exposure ratio

The major difficulty with the extrapolation method is to determine the smoker/never smoker exposure ratio. Ideally, the exposure ratio is based on carcinogenically equivalent exposures, such that one unit of exposure for a never smoker has the same lung cancer risk as one unit of exposure for an active smoker. However, no carcinogenically equivalent measure of exposure exists because smokers and never smokers inhale different types of tobacco smoke. Smokers mostly inhale mainstream smoke produced at temperatures above 600 °C and then drawn through the cigarette and filter, whereas the ETS inhaled by never smokers consists mostly of sidestream smoke formed between puffs at 350 °C and, partly, of exhaled mainstream smoke. Due to the different combustion temperatures, the amount of specific carcinogens in mainstream and sidestream smoke differs. For example, measurements of two brands of modern filter cigarettes find that fresh sidestream smoke contains 42 times more N-nitrosodimethylamine and 1.5 times more benzo(a)pyrene, but 15% less catechol (a major cocarcinogen (Hecht *et al.*, 1981)) and 70% less N-nitrosonornicotine, by weight, than mainstream smoke (Adams *et al.*, 1985). The problem of the relative carcinogenicity of mainstream and sidestream smoke is exacerbated by the possibility of substantial differences in the composition of their gaseous and particulate phases; however, this has not been studied adequately. Overall, the relative carcinogenicity per unit weight of mainstream and sidestream smoke is not known, though there is some evidence to indicate that particulate sidestream smoke is more carcinogenic than mainstream smoke. An animal study cited by Wynder and Hoffman (1967) finds more skin cancers among shaved mice painted with particulate sidestream versus mainstream condensates. A series of four Ames mutagenicity assays finds particulate sidestream smoke to be over ten times more mutagenic than an equivalent amount, by weight, of mainstream smoke in one test series, though there is little difference in the other three tests (Lofroth & Lazaridis, 1986).

In the absence of a measure of the carcinogenicity of mainstream and sidestream smoke, this study uses the current and never smoker's retained exposure to particulate ETS to estimate the smoker/never smoker exposure ratio. The exposure estimate adjusts for the dilution of sidestream smoke by ambient air. As a first approximation, the carcinogenicity of mainstream and sidestream particles is assumed to be equal (the effect of assuming a greater carcinogenicity for sidestream smoke is discussed later). Exposure to the gas phase of mainstream and sidestream smoke is not included because exposure to the gas phase, without concurrent exposure to tobacco smoke particulates, has not been found to cause lung cancer (Hoffmann *et al.*, 1978; SG, 1982). However, it is possible that future research may establish a significant carcinogenic role for the gas phase.

The smoker/never smoker exposure ratio is also based on the retained exposure (the amount of particulate by weight deposited in the lungs) instead of the inhaled exposure. A significant proportion of the latter is immediately exhaled and, consequently, has no effect on carcinogenesis. Hiller *et al.* (1982) experimentally determine in 11% particulate retention rate for never smokers exposed to sidestream smoke. Similar results have been found for other particulates in the size range of sidestream smoke (Davies *et al.*, 1972; Heyder, 1982). Conversely, the average active smoker retains between 47% and 96% of inhaled mainstream smoke, with most estimates falling above 70% (Dalhamm, 1968; Hoegg, 1972; Corn, 1974; First, 1984). The higher deposition rate for active smokers is thought to result either from deeper inhalation (Muir, 1974), hygroscopic growth and coagulation (Hiller *et al.*, 1982), or from electrical charges in mainstream smoke (Stober, 1984).

ETS exposure and cotinine. Tobacco smoke exposure can also be determined from blood, urine or saliva levels of cotinine — a nicotine metabolite. Cotinine appears, at first, to be a more accurate measure of exposure than retained particles. The latter can only be indirectly estimated for never smokers from exposure to all respirable particles, which include dust, pollen, and other aerosols. In contrast, cotinine is an accurate and specific indicator of tobacco smoke exposure because it is the only important source of exposure to nicotine. Cotinine also measures dose (the amount of a tobacco constituent metabolized by the body), whereas an estimate of retained particles only measures exposure. Unfortunately, though several studies show that cotinine levels in body fluids can accurately differentiate between never smokers with high, moderate and low ETS exposure (Jarvis *et al.*, 1984; 1985) or between nonsmokers and current smokers (Wald *et al.*, 1984), cotinine levels in never and current smokers are not directly comparable. This is

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Table 1. Estimated number of never, ex-, and current smokers ≥ age 35 in 1980 in the U.S.*

	Men		Women		
Smoking Status	Number	Percent	Number	Percent	Total
Never	11,960,000	27.03	28,846,000	55.66	40,806,000
Ex-	15,314,000	34.62	7,774,000	15.00	23,088,000
Current	16,965,000	38.35	15,201,000	29.34	32,166,000
Total	44,239,000	100.00	51,821,000	100.00	

*Based on U.S. Census figures for the total male and female population ≥ 35 years of age (USDC, 1982) and the percentage of never smokers, ex-smokers and current smokers of all races ≥ 35 from the 1979/1980 National Health Interview Survey.

partly because the half-life of cotinine is substantially shorter for current than never smokers (Kyerematen *et al.*, 1982; Lynch, 1984; Sepkovic *et al.*, 1986), so that cotinine levels could underestimate the relative exposure received by the lungs of smokers. However, the major problem with using cotinine to determine relative exposures is due to the occurrence of nicotine in a protonated form in the particulate phase of the mainstream smoke inhaled by smokers but in an unprotonated form in the gas phase of the sidestream smoke inhaled by nonsmokers (Eudy *et al.*, 1986; IARC, 1985). Consequently, cotinine or nicotine levels in smokers measure the lung's particulate exposure, whereas these levels in nonsmokers largely measure nasal and pharyngeal exposure to gas phase constituents with a similar retention rate to that of nicotine. The two estimates of exposure are not comparable because they differ both by site and type of exposure. Nonsmokers should also absorb a higher percentage of inhaled nicotine than smokers because the unprotonated nicotine of sidestream smoke is absorbed more rapidly than the protonated nicotine of mainstream smoke (IARC, 1985).

Data Sources and Assumptions

Though superficially simple, the calculation of each of the four preliminary estimates is based on a large number of estimated parameters. These parameters are obtained from published data and analyses of the 1970 (NCHS, 1970) and 1979/1980 National Health Interview Surveys (NCHS, 1981). Due to the large sample size of the National Health Interview Surveys (the 1970 and 1979/1980 NHIS contain smoking data for a sample of 74,451 and 37,604 individuals ≥ 17 years of age, respectively), these surveys provide the best available estimates of the number of never, ex-, and current smokers by occupation, age, and sex (Table 1). Studies of ambient particulate ETS levels in white-collar workplaces in the U.S. are identified from the Building Performance Database, an on-line database accessible through national data networks (Sterling *et al.*, 1985). Most of the identified studies were conducted by the National Institute for Occupational Safety and Health.

All four preliminary estimates are based on estimated average exposures and risks for never and current smokers in 1980. The best exposure-based risk estimate would compare cumulative lifetime exposure for never and ever smokers, because the lifetime exposure of many ex-smokers exceeds that of current smokers. Unfortunately, no cumulative lifetime exposure data for a representative sample of ever and never smokers exists. The estimated risk and the number of excess lung cancer deaths are given for never smokers age 35 and over because almost all lung cancer deaths occur in this age group. However, the average exposure is calculated for never smokers ≥ 17 years of age. ETS exposure is more frequent among young adults (Friedman *et al.*, 1983), and this early exposure could latently affect the lung cancer risk.

In addition to many minor assumptions concerning the accuracy and representativeness of the data, the final estimate of the number of never smoker lung cancer deaths from exposure to particulate ETS is based on four major assumptions:

1. The carcinogenicity of tobacco smoke depends upon exposure to the particulate phase,
2. The lung cancer risk per unit exposure to mainstream and sidestream particulate tobacco smoke is the same,
3. The relationship between risk and each unit of exposure is approximately linear, and
4. There is no low exposure threshold where the lung cancer risk falls to zero.

Calculation of the Linear Extrapolation Estimate

The following three sections calculate the average particulate ETS exposure for never smokers and current smokers as well as the lung cancer risk for current smokers. The population of never smokers, estimated from the 1979/1980 National Health Interview Survey, is given in Table 1.

Never Smoker's Average Particulate ETS Exposure

Almost all particulate ETS exposure occurs indoors

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Table 2. Estimated time budgets (hours/day)[a] in 1980 in the U.S.

Location	Employed Women	Employed Men	Housewives	All Women	All Men
In homes (their own and others)	16.3	14.1	21.3	18.6	15.7
Workplace	4.7	6.1	0.0	—	—
Places of business and other locations	1.3	1.4	1.5	1.5	1.3
Restaurants and bars	0.3	0.5	0.1	0.2	0.4
Outside of homes and in transit	1.4	1.9	1.1	—[b]	—
	24.0	24.0	24.0		

[a]The 1965 data from Szalai (1972) are adjusted to account for a 9% drop in the average hours worked between 1965 and 1980 (USDC, 1981). The reduction in work time, 0.6 hours for men and 0.5 hours for women, is divided among the time spent in the four other locations.
[b]No exposure is assumed for this category.

because of low indoor ventilation rates and because adults spend over 85% of their time indoors (Szalai, 1972). The average never smoker's exposure to particulate ETS depends on 1) the average inhalation rate and, for each indoor location, 2) the time spent there, 3) the average particulate ETS level, and 4) the proportion of never smokers exposed.

1. Inhalation rate

Data from Altman and Ditmer (1971) indicate an average inhalation volume of 1.08 m^3/hour for men and 0.62 m^3/hour for women, based on the average volume of air inhaled at rest and during light work.

2. Time spent in five locations

The results of a 1965 44-city time budget study (Szalai, 1972) are used to estimate the average daily time spent by never smokers in five locations; home, work (including time before and after work and during lunch), places of business and other locations, restaurants and bars, and outside the home and in transit. The time spent in restaurants and bars is determined separately, because they sometimes have very high ambient particulate ETS levels. Unfortunately, the original data do not permit dividing time into indoor and outdoor hours — time spent in both "places of business and other locations" and "outside of home and in transit" includes indoor and outdoor locations. To simplify matters, we assume that all time spent in "places of business and other locations" is indoor time where particulate ETS exposure occurs and all time spent "outside of home and in transit" is outdoor time with no particulate ETS exposure.

Table 2 estimates the average time spent in each location by employed men, employed women, and housewives. The time budget for housewives is used to estimate the time budget for all nonemployed men and women ("nonemployed" includes individuals actively seeking work, homemakers, and retirees). Time spent in nonwork locations is adjusted for the proportion of nonemployed adults because, according to time budget results, housewives spend more time in places of business and less time in restaurants and bars than do employed individuals. The 1979/1980 National Health Interview Survey estimates that 19.1% of male and 49.2% of female never smokers are nonemployed. Table 2 also gives the employment-weighted time spent in each nonwork location.

3. Indoor particulate ETS levels

Indoor particulate ETS exposure is indirectly estimated from on-site measurements of total or respirable suspended particles. This method requires an adjustment for background (nonsmoking-related) particulate levels. Background measurements should be taken indoors when no one has smoked for several hours but when all other conditions are the same as during periods of smoking (these criteria are rarely met). If there are no indoor background measurements, outdoor measurements are used as a crude estimate of the indoor particulate level in the absence of smoking.

Estimated particulate ETS levels in restaurants and bars. The average particulate level (unadjusted for background levels) in 27 restaurants, bars and entertainment facilities is 0.30 mg/m^3 (see Table 3). The average indoor particulate ETS level, after adjusting for the average background particulate level of 0.04 mg/m^3, is 0.26 mg/m^3.

Estimated particulate ETS levels in places of business. The estimated average particulate ETS level in offices (see below) is also used for the time budget category "places of business and other locations" (banks, shopping centers, etc.).

Estimated particulate ETS levels in the workplace. Workplace particulate levels are available for restaurants, bars, offices, and service buildings. It is impossible to estimate particulate ETS exposures from particulate levels in indoor blue-collar workplaces because of high background particulate levels from industrial activities. The average particulate ETS exposure should be less for blue-collar than white-collar never smokers because blue-collar workplaces, compared to offices, are better ventilated in order to re-

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Table 3. Particulate levels (mg/m³) in bars, restaurants and entertainment facilities in the U.S.

Reference	Premise	Measurement Type	#	Mean	Background (# measurements)
Cuddeback *et al.*, 1976	2 Taverns	TPM[a]	5	0.445	(none)
Elliot & Rowe, 1975	3 Arenas	TPM	19	0.367	0.07 (2 indoors)
First, 1984	3 Taverns	nd[b]	nd	0.543	(none)
	3 Restaurants	nd	nd	0.220	(none)
Repace & Lowrey, 1980	17 Entertainment facilities[c]	RSP[d]	20	0.243	0.04 (4 indoors)
			Average:[e]	0.30	
		Adjusted for background levels:[f]		0.26	

[a]Total particulate matter.
[b]No data given.
[c]Three bars, seven restaurants, and one each of a lodge, bar and grill, firehouse bingo game, church bingo game, inn, bowling alley, and an arena. Active smoking occurred during the time of all measurements.
[d]Respirable suspended particles.
[e]The average is determined by weighting for the number of premises in each study.
[f]Adjusted for Repace and Lowrey's (1980) background level of 0.04 mg/m³. The background level of Elliot and Rowe is not used because it is for arenas which make up only a small proportion of high exposure workplaces.

duce dust and fume exposure and because smoking is prohibited in a higher percentage of blue-collar workplaces (NICSH, 1978). However, we assume that exposed blue-collar workers receive the same particulate ETS exposure as white-collar office workers.

Table 4 summarizes the results of twenty studies of particulate levels in office or service buildings in the U.S. The mean total and respirable particulate levels are 0.08 mg/m³ and 0.068 mg/m³, respectively. The overall mean particulate level, ignoring the difference between total and respirable particulates, is 0.076 mg/m³. The mean level, limited to twelve studies where active smoking was reported to occur during the time of measurement, is also 0.076 mg/m³.

Outdoor background levels, reported by seven studies, average 0.053 mg/m³ and range from 0.01 to 0.1 mg/m³. The indoor background level in the absence of active smoking is 0.035 mg/m³ in two studies of offices (Parker *et al.*, 1983; Collett, 1985) and 0.037 mg/m³ in one study of an office and two libraries (Repace and Lowrey, 1980).

The minimum background outdoor particulate level of 0.01 mg/m³ is used to conservatively estimate the indoor particulate ETS level because indoor particulate levels for 13 studies are below the outdoor average of 0.053 mg/m³ while in eight studies the indoor particulate level is below the indoor background level of approximately 0.035 mg/m³. Therefore, up to 0.066 mg/m³ (0.076–0.01) of airborne particles in office and service buildings could be from tobacco smoke, assuming no other indoor sources of particles.

Estimated particulate ETS levels in residences. Five field studies measure the effect of at least one smoker on the 24-hour particulate level in residences. Table 5 shows that one smoker increases the hourly particulate level over background levels (homes with no smokers) by an average of 0.015 mg/m³, while two smokers increase the particulate level by an average of 0.042 mg/m³. The latter average is assumed to represent all residences with two or more smokers.

The average home exposure is weighted by the proportion of never smoking respondents to the 1970 National Health Interview Survey who reported living with one versus two or more smokers. The weighted average hourly particulate ETS level in the residences of never smokers is approximately 0.02 mg/m³ for both sexes.

4. Proportion of never smokers exposed in each location

All never smokers are assumed to be exposed in "restaurants and bars" and "places of business and other locations." The proportion exposed at work is estimated from the occupational distribution of never smokers while the proportion exposed at home is estimated from the proportion of never smokers who report living with a current smoker (spouse, relative, friend, etc.).

Proportion of never smokers exposed at work. Table 6 gives the 1979/1980 National Health Interview Survey employment distribution of never smokers age 17 and older. Occupations are grouped by the likelihood of particulate ETS exposure. Students are categorized as working in indoor white-collar environments, while blue-collar workers are separated into outdoor and indoor workers. All white-collar, indoor blue-collar, and restaurant and bar employees are assumed to be exposed to particulate ETS at work, while nonemployed individuals and outdoor workers are assumed to receive no workplace exposure. In total, 66.7% of all male and 49.3% of all female never smokers are estimated to be exposed to particulate ETS at work.

Proportion of never smokers exposed at home. The

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Table 4. Particulate levels (mg/m³) in white-collar workplaces in the U.S.

Reference	Use	Building Smoking[a]	Employees[b]	Measurement Type	#	Length	Date	Mean
Blake *et al.*, 1981	Store	nd	nd	TPM	10	nd	Nov/79	0.019
Chrostek, 1979	Office	nd	30	RSP[c]	1	7 hr	May/79	0.030
Chrostek & Moshell, 1982	Office	nd	100	TPM	5	8 hr	Aug/81	0.120
Collett, 1985	Office	Y	6[d]	RSP	8	40 min	Jul/85	0.050
Cornwell *et al.*, 1981	Office	Y	>100	RSP	28	2 min	Nov/80	0.048
Gorman, 1980	Office	nd	6	TPM	nd	nd	Jul/80	0.11[e]
Gunter & Thoburn, 1985	Office	nd[f]	nd	TPM[g]	7	6.5 hr	Nov/84	0.164
Hicks, 1981a	Office	Y	nd	nd	3	nd	Mar/80	0.047
Hicks, 1981b	Office	nd	40	TPM	2	6 hr	Dec/80	0.055
Hodgson & Morley, 1983	Office	nd	41	RSP	3	nd	Mar/83	0.025
Hollett, 1979	Office	nd	nd	TPM	21	nd	Jul/79	0.143[h]
Moschandreas *et al.*, 1980	Office	Y	150	TPM	3	24 hr	nd	0.030[i]
	Office	Y	100	TPM	3	24 hr	nd	0.038[j]
Neal *et al.*, 1978	Hospital	Y	nd	TPM	41	48/hr	Aug–Feb	0.030
Parker *et al.*, 1983	Office	Y	100	TPM	2	8 hr	Feb/83	0.032
	Office	Y	16	TPM	3	8 hr	Feb/83	0.094
Repace & Lowrey, 1980	Hospital waiting room	Y	nd	RSP	1	12 min	Mar	0.187
Salisbury, 1979	Stock Exchange	Y	nd	TPM	3	5 hr	Oct/78	0.287
Salisbury *et al.*, 1982	Office	Y	500	TPM	8	6 hr	Mar/81	0.038
Tharr, 1980	Office	nd	100	TPM	2	7 hr	Jun/80	0.060
Thompson *et al.*, 1973	2 stores	nd	nd	TPM	nd	nd	Nov/71	0.083
Turiel *et al.*, 1981	Office	Y	nd	TPM	nd	12 hr	nd	0.031
							Average:	0.076
			Adjusted for Background Level (see text):					0.066

[a]Active smoking while particulate levels were sampled.
[b]On the floor(s) where measurements taken.
[c]Respirable suspended particles.
[d]In immediate area of sampler, two of the six staff were smokers.
[e]Close to office copier.
[f]No data given.
[g]Total particulate matter.
[h]Major construction site across the street.
[i]Based on 24 hour sample. Maximum recorded 0.057 mg/m³.
[j]Based on 24 hour sample. Maximum recorded 0.130 mg/m³.

Table 5. Effect of smoking on 24-hour respirable suspended particle (RSP) levels (mg/m³) in residences in the U.S.

Reference	Mean RSP Level in Homes with No Smokers	1 Smoker	2 Smokers	Increase due to 1 Smoker	2 Smokers
Spengler *et al.*, 1981	0.024	0.037	0.052	0.012	0.027
EPRI, 1984	0.024	0.043	0.075	0.019	0.051
Hosein & Corey, 1986[a]	0.038	0.053	0.080	0.015	0.042
Lebowitz *et al.*, 1984	0.018	0.033[b]	—	0.015	—
Spengler *et al.*, 1985	0.028	—	0.074[b]	—	0.046
			Average:	0.015	0.042

[a]Average of reported winter and summer means.
[b]Number of resident smokers not given in reference. The results have been assigned to the most probable category, on the basis of the results of the other studies.

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Table 6. 1979/1980 National Health Interview Survey estimate of the occupational distribution of never smokers ≥ age 17 in the U.S.

Occupation	Men (%)	Women (%)
Indoor white-collar[a]	43.3	41.0
Indoor blue-collar[b]	21.6	6.2
Restaurants and bars[c]	1.8	2.1
Outdoor workers[d]	14.2	1.5
Not employed[e]	19.1	49.2
	100.0	100.0

[a]Includes students and professional, managerial, technical, clerical and service occupations.
[b]Includes industrial and warehousing occupations.
[c]Includes waiters and waitresses, entertainers, bartenders, busboys, recreation and amusement attendants, pub and food service workers.
[d]Includes construction, agriculture, forestry and fishing occupations.
[e]Includes retired, homemakers and unemployed.

1970 National Health Interview Survey estimates that 29.6% of male and 35.7% of female never smokers age 17 and over live with a current smoker. Since the 1979/1980 National Health Interview Survey does not include smoking information for all household members, it cannot be used for this purpose. However, using data for 1970 should overestimate the proportion of never smokers exposed at home in 1980 because the number of active smokers has declined 6% for men and 2% for women between 1970 and 1980 (Weinkam & Sterling, 1987).

Estimated particulate ETS exposure

Table 7 summarizes the average never smoker's inhalation exposure to particulate ETS. The average daily inhaled particulate ETS exposure is 0.62 mg for male and 0.28 mg for female never smokers. The daily retained particulate ETS exposure, based on an 11% retention rate, is 0.07 mg for male and 0.03 mg for female never smokers.

Current Smoker's Average Exposure

The average smoker's daily exposure to particulate tobacco smoke is assumed to equal the average number of cigarettes per day consumed multiplied by the average tar delivery per cigarette. For simplicity, the current smoker's particulate ETS exposure is not included because it is only a small fraction of the current smoker's total particulate tobacco smoke exposure. An average consumption of 29.3 cigarettes per day for current smokers is calculated by dividing the 1979/1980 average of 626.5 billion cigarettes sold in the U.S. (Maxwell, 1981) by the 1979/1980 National Health Interview Survey estimate of 58.5 million current smokers age 17 and over. The average of 29.3 cigarettes per day is used for both sexes because there is little difference in the 1979/1980 National Health

Table 7. Estimate of the average never smoker's inhalation exposure of particulate environmental tobacco smoke (ETS) (mg/day) in 1980 in the U.S.

Location	Respiration Rate/hour	Ambient ETS mg/m³	Hours of Exposure	Proportion Exposed	Weighted Exposure
Men					
Home	1.08	0.02	15.7	0.296	0.100
Rest/Bar[a]	1.08	0.26	0.4	1.000	0.112
Other[b]	1.08	0.066	1.3	1.000	0.093
Work					
White-collar	1.08	0.066	6.1	0.433	0.188
Blue-collar	1.08	0.066	6.1	0.216	0.094
Rest/Bar	1.08	0.26	6.1	0.018	0.031
No Workplace Exposure[c]	—	—	—	0.333	0.000
					Total 0.62
Women					
Home	0.62	0.02	18.6	0.357	0.082
Rest/Bar	0.62	0.26	0.2	1.000	0.032
Other	0.62	0.066	1.5	1.000	0.061
Work					
White-collar	0.62	0.066	4.7	0.410	0.079
Blue-collar	0.62	0.066	4.7	0.062	0.012
Rest/Bar	0.62	0.27	4.7	0.021	0.016
No Workplace Exposure	—	—	—	0.501	0.000
					Total 0.28

[a]Restaurants and bars.
[b]Places of business and other locations.
[c]Unemployed, retired, homemakers, and outdoor workers.

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Table 8. National Mortality Followback Survey estimate of the number of lung cancer deaths (LCD) among never smokers in the U.S. in 1980

Age	LCD/100,000[a]	Never Smokers (100,000)[b]	Estimated LCD
Men			
35–44	2.3	37.08	85.3
45–54	3.5	25.68	89.9
55–64	33.4	22.91	765.2
65–74	63.8	19.80	1,263.2
75–84	87.9	11.05	971.3
85+	100.0[c]	3.04	304.0
			Total: 3,479
Women			
35–44	0.4	62.60	25.0
45–54	2.8	61.30	171.6
55–64	10.9	61.30	668.2
65–74	18.7	55.96	1,046.5
75–84	48.4	36.87	1,784.5
85+	60.0[c]	10.27	616.2
			Total: 4,312

[a]From Enstrom & Godley (1980).
[b]Estimated from the 1979/1980 National Health Interview Survey age distribution of never smokers of all races and the U.S. Census (USDC, 1982) estimate of the population in 1980.
[c]Estimated from the American Cancer Society study (Garfinkel, 1981) as the rates for this age group were not given by the National Mortality Followback Survey (Enstrom & Godley, 1980). The American Cancer Society never smoker lung cancer rates are 94.8 for men and 52.4 for women 85–89 years of age. These rates are increased slightly to account for higher rates among people older than 89 and for the higher incidence of occupational exposures for the entire U.S. population.

Interview Survey estimate of the average consumption by sex; the average female smoker consumes 96% of the average for male smokers.

The 1980 sales-weighted average tar delivery per cigarette, excluding particulate nicotine, is 13.2 mg/day (Tobacco Institute, 1981). This average is used in the risk estimates for men. However, data from the American Cancer Society study show that women inhale approximately 20% less than men (Hammond, 1966). We assume that women in 1980 still inhale 20% less than men, and are thus exposed to 10.6 mg/day. The average daily particulate tobacco smoke exposure is, consequently, 387 mg for male and 311 mg for female smokers. The daily retained exposure, based on an 80% retention rate, is 310 mg for male and 249 mg for female smokers, excluding exposure to ETS.

Current Smoker's Average Lung Cancer Rate

In 1980 there were 75,362 male and 28,210 female lung cancer deaths among individuals age 35 and over (NCHS, 1986). The number of lung cancer deaths among current smokers cannot be directly determined because the smoking status of decedents is not noted on death certificates. The number of current smoker lung cancer deaths from tobacco smoke exposure is obtained by subtracting, from the total number of lung cancer deaths, an estimate of the number of lung cancer deaths among never smokers, ex-smokers, and current smokers due to nonsmoking causes.

Lung cancer deaths among never smokers

Age-specific lung cancer death rates are available for white never smokers from the National Mortality Followback Survey (Enstrom & Godley, 1980). The use of these rates assumes indentical rates for nonwhites and no change in the lung cancer death rate for never smokers between 1966–1968 and 1980. These lung cancer death rates, multiplied by the age-specific number of never smokers in 1980, estimate 3,479 male and 4,312 female never smoker lung cancer deaths in the U.S. in 1980 (Table 8).

Lung cancer deaths among ex-smokers

The number of lung cancer deaths among the 23.09 million ex-smokers in 1980 is estimated from the average lung cancer relative risk for current versus ex-smokers in two cohort studies: the American Cancer Society study (Hammond, 1964) and the U.S. Veterans study (Rogot & Murray, 1980). The male risk ratios are also used for women because none of the cohort studies reports the risk for all ex- and current female smokers.

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The average lung cancer risk for all current versus all ex-smokers is 2.26, based on a risk of 1.67 in the American Cancer Society study and 2.85 in the Veterans study. The average ratio of 2.26, combined with the 1979/1980 National Health Interview Survey estimates of the number of current and ex-smokers, predicts 20,517 male and 4,410 female ex-smoker lung cancer deaths.

The difference in the risks for ex-smokers compared to current smokers in the two studies is probably due to the higher percentage of long-term ex-smokers, with lower lung cancer rates than short-term ex-smokers, in the Veterans study. All ex-smokers in the Veterans study had not smoked for a minimum of twelve years compared to a minimum of 34 months for ex-smokers in the American Cancer Society study. The American Cancer Society results may be more appropriate here because the National Health Interview Survey estimate of the number of ex-smokers includes both short and long-term ex-smokers.

Current smoker lung cancer deaths not attributable to smoking

The number of nonsmoking-attributable current smoker lung cancer deaths is estimated by assuming that smokers would experience the mortality rates of the National Morality Followback Survey never smokers if they did not smoke. These mortality rates, applied to the 1979/1980 National Health Interview Survey estimate of the sex and age-specific population of current smokers, estimate 3,111 male and 1,094 female lung cancer deaths.

Smoking attributable lung cancer risk for current smokers

The number of smoking-attributable lung cancer deaths among male current smokers over 35 is 48,255, obtained from subtracting 3,479 never smoker, 20,517 ex-smoker, and 3,111 nonsmoking-attributable lung cancer deaths among current smokers from the 1980 total of 75,362 male lung cancer deaths. The same method estimates 18,394 smoking-attributable lung cancer deaths among female current smokers over 35 in 1980. Given 16.965 million male and 15.201 million female current smokers over 35 in 1980, this estimates a smoking-attributable lung cancer risk of 284 lung cancer deaths (LCD)/100,000 male and 121 LCD/100,000 female current smokers over age 35. Repace and Lowrey (1985) estimate a rate of 316 LCD/100,000 male or female smokers for use in their linear extrapolation estimate. However, they assume that all smoking-attributable lung cancer deaths occur among current smokers only (no deaths among ex-smokers), they do not adjust for occupational or other causes of lung cancer among smokers, and they include cancers of the larynx and other non-lung sites.

Lung Cancer Risk for Never Smokers From Particulate ETS Exposure

The estimated daily retained exposure is 310 mg for male and 249 mg for female current smokers and 0.07 mg for male and 0.03 mg for female never smokers. The male smoker's retained exposure is 4,429 times greater than the average male never smoker's retained exposure. Given a smoking-attributable lung cancer death rate for male current smokers of 284 LCD/100,000, the average male never smoker's lung cancer risk is 0.064 LCD/100,000, which predicts approximately 8 lung cancer deaths from exposure to particulate ETS among the 11.96 million male never smokers in 1980. The same method estimates a risk of 0.015 LCD/100,000 female never smokers, which predicts 4 lung cancer deaths from exposure to particulate ETS among the 28.85 million female never smokers in 1980.

Reliability of the Estimate

The linear extrapolation estimate of 12 never smoker lung cancer deaths in 1980 from exposure to particulate ETS is based on a large number of unverifiable assumptions and parameter estimates. Due to the large number of assumptions, it is neither meaningful nor possible to calculate upper and lower confidence limits. However, the reliability of each of the four preliminary estimates is assessed below. Evidence indicates that several of the preliminary estimates are more likely to result in an overestimate rather than an underestimate of the true number of never smoker lung cancer deaths. However, a plausible upper estimate is calculated for three of the four preliminary estimates. These upper estimates are used to calculate a maximum final estimate, given the major assumptions of the linear extrapolation method.

Number of Never Smokers

The final estimate of the number of never smoker lung cancer deaths increases if the estimated number of never smokers increases. The present estimate of 11.96 million male and 28.85 million female never smokers is based on self-reported smoking status, and is probably an overestimate of the number of never smokers. Two-stage interview studies show that approximately 5% of self-reported never smokers are actually ex- or current smokers (NRC, 1986). For this reason, the estimated number of never smokers is not increased when calculating the upper estimate.

Never Smoker's Average Exposure

The estimated number of never smoker lung cancer deaths increases if the average never smoker's exposure increases. Several factors suggest that our estimated exposure *overestimates* the true exposure. For

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example, many of the measurements of total or respirable particles are for workplaces which probably had higher than average particulate ETS levels. Most buildings in the Building Performance Database were studied in response to occupant complaints about "building illness" or poor indoor air quality. Even though tobacco smoke may not be an important factor in building illness (Sterling *et al.*, 1987), it could affect the occupants' perception of the air quality and lead to more complaints in buildings with high versus low particulate ETS levels. In addition, all indoor blue- and white-collar workers are assumed to be exposed to particulate ETS at work, even though smoking is prohibited in 11% of white- and 28% of blue-collar workplaces (NICSH, 1978). Interview studies also show lower workplace exposure rates than the estimated rate of 66.7% for male and 49.3% for female never smokers. For example, only 29.4% of the control group of female never smokers in a case-control study report workplace exposure during the past 25 years (Garfinkel *et al.*, 1985). In a 1979/1980 questionnaire survey of 37,881 never smokers, only 40.4% of both sexes combined reported ETS exposure in "small spaces" such as at work (Friedman *et al.*, 1983).

Two field studies contain enough information to calculate the average inhaled particulate ETS exposure for men. Both of these studies estimate average particulate ETS exposures that are within six percent of the comparable estimates given in Table 7. The studies use personal monitors, carried by subjects for several days, to determine average exposures to respirable suspended particles. The difference between the average personal and background (outdoor) exposures to respirable suspended particles in a study of 48 subjects, none of whom live with a smoker, is 0.019 mg/m^3 (Sexton *et al.*, 1984). If particulate ETS accounts for all of the difference in respirable suspended particles, then the average 24-hour particulate ETS exposure at a male respiration rate of 1.08 m^3/hour, is 0.49 mg/day. For comparison, our estimate of the average daily inhaled exposure of male never smokers with no home exposure is 0.52 mg/day (see Table 7). Spengler *et al.* (1985) determine personal exposures to respirable suspended particles for 101 volunteers in two industrial towns in Tennessee. The difference between the average personal exposure and the background (outdoor) level is 0.024 mg/m^3. This predicts an average daily particulate ETS exposure of 0.62 mg/day, which is identical to our estimate for men.

Repace and Lowrey (1985) estimate an average inhaled exposure for either sex of 1.43 mg/day, based on modeling indoor smoking, occupancy, and ventilation rates, which is 3.18 times the average of our estimates for men and women. There are several possible causes for the difference. For example, Repace and Lowrey assume that all never smokers are actively employed and, therefore, possibly exposed at work. In contrast, the 1979/1980 National Health Interview Survey estimates that approximately 40% of all never smokers are not employed. Furthermore, Repace and Lowrey calculate the average ambient ETS level in the workplace from the average of modeled levels in low-exposure and high-exposure workplaces. Their model estimates an ambient particulate level (from tobacco smoke alone) of 0.17 mg/m^3 for low-exposure workplaces such as offices and of 0.42 mg/m^3 for high-exposure workplaces. The particulate level for the latter is representative of measured levels in very smoky workplaces such as taverns, bars, and dance halls. The average for the two types of workplaces is 0.30 mg/m^3, which is higher than all of the measured levels for white-collar workplaces (see Table 4) and higher than the average for restaurants, bars and other entertainment facilities (see Table 5). It may not be appropriate to average the estimate for low and high-exposure workplaces, because the 1979/1980 National Health Interview Survey estimates that approximately twenty times as many never smokers work in low-exposure workplaces such as offices than in high-exposure workplaces such as bars and taverns.

There is no plausible average upper estimate for the inhaled exposure which is substantially greater than the estimates given in Table 7, which is also based on field measurements of ambient particulate levels. However, an arbitrary upper estimate can be made by doubling the previous estimates. Thus, the upper inhaled estimates are 1.24 mg/day for male and 0.56 mg/day for female never smokers. These give average retained exposures of 0.14 mg/day for male and 0.06 mg/day for female never smokers.

Current Smoker's Average Exposure

The estimated number of never smoker lung cancer deaths increases if the average smoker's true exposure, derived from the average tar delivery per cigarette multiplied by the average cigarette consumption, is *less* than estimated.

The average tar delivery per cigarette is based on machine smoked deliveries. The machine smoking standard of one two-second 35 ml puff/minute was established over 30 years ago to reflect the smoking habits of that time. Since then, several studies indicate that smokers partially compensate for a decline in the nicotine delivery per cigarette by smoking each cigarette more intensely (Ashton *et al.*, 1979; Herning *et al.*, 1981; Hill & Marquardt, 1980; Russell *et al.*, 1975). This is done by increasing the average puff frequency and/or volume or by inhaling more deeply. The probable increase in the intensity with which cigarettes are smoked indicates that the estimated exposure for current smokers is more likely to *underestimate* than overestimate the true exposure.

Conversely, the average consumption of 29.3 ciga-

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rettes per day is based on sales data for the number of cigarettes sold in 1980 divided by the 1979/1980 National Health Interview Survey estimate of the number of current smokers. Estimates based on interviews with current smokers are not used because smokers significantly underreport their cigarette consumption (Todd, 1978). However, the estimate of 29.3 cigarettes per day may be too high because the 1979/1980 National Health Interview Survey excludes smokers under age 17 and because some of the self-reported never and ex-smokers should be current smokers (NRC, 1986). If the probable increase in smoking intensity is ignored, an increase in the estimated number of current smokers by 10% (to account for smokers under age 17 and misclassified never smokers) decreases the average daily retained exposure from 310 mg to 283 mg for male and from 249 to 228 mg for female current smokers. This is further decreased to 166 mg for male current smokers and to 134 mg for female current smokers by using the lowest experimentally determined particulate retention rate of 47% (First, 1984) instead of an 80% retention rate.

Current Smoker's Average Lung Cancer Rate

The estimated number of never smoker lung cancer deaths increases if the lung cancer risk for current smokers increases. This occurs if the estimated number of lung cancer deaths decreases among (1) ex-smokers, (2) never smokers, and (3) current smokers who die from causes other than smoking. This is calculated for the latter two groups by using the American Cancer Society never smoker lung cancer death rates (Garfinkel, 1981) instead of the rates from the National Mortality Followback Survey. The American Cancer Society rates were not used before because they are for an unrepresentative group of mostly middle-class individuals (Hammond & Seidman, 1980), whereas the National Mortality Followback Survey rates are based on a representative sample of all never smoker lung cancer deaths. The number of ex-smoker lung cancer deaths is minimized if the ex-smoker/smoker mortality ratio from the Veterans study (Rogot & Murray, 1980) is used instead of the average for the American Cancer Society and Veterans studies combined.

These three changes increase the estimated number of current smoker lung cancer deaths from 48,255 to 55,902 male deaths and from 18,394 to 19,954 female deaths. However, this only slightly alters the lung cancer risk because the revised estimate of the average smoker's exposure depends upon increasing the number of smokers by 10%. Given a 10% increase in smokers, the lung cancer rate increases 5.6% to 300 LCD/100,000 male never smokers, but falls 1.7% to 119 LCD/100,000 female never smokers.

The lung cancer death rate for female current smokers is substantially less than the rate for male current smokers. The difference could partly be caused by women inhaling less deeply than men or by smoking lower tar cigarettes. Alternatively, the lower mortality rate for women could reflect a shorter latency period because women, on average, took up smoking at a later date than men. An upper estimate of the lung cancer death rate for female smokers can be adjusted for this by assuming that the risk/mg of exposure for women is equal to the risk/mg of exposure for men. This estimates a risk of 242 LCD/100,000 female smokers.

Upper Risk Estimate

The upper estimate is 62 lung cancer deaths among never smokers as a result of exposure to particulate ETS. This is based on a lung cancer death rate of 300 LCD/100,000 male and 242 LCD/100,000 female current smokers, an average retained exposure of 166 mg/day for male and 134 mg/day for female current smokers, and a retained exposure of 0.14 mg/day for male and 0.06 mg/day for female never smokers.

Comparison with Other Estimates

The linear extrapolation estimate of 12 deaths, or the upper linear extrapolation estimate of 62 never smoker lung cancer deaths, is substantially less than five alternative estimates, ranging from 265 to 3,610 lung cancer deaths, given in Table 9. All of the alternative estimates use the National Health Interview Survey estimate of the number of never smokers $\geq$ 35 years of age. Three of the alternatives are risk-based estimates derived from the results of epidemiological studies: one from the difference in lung cancer mortality rates between Seventh-Day-Adventists and other never smokers (termed a phenomenological estimate by the authors), and the other two apply average geometric mean lung cancer risks observed in epidemiological studies to the population-attributable risk equation (Cole & MacMahon, 1971). The two remaining estimates are exposure-based estimates derived from smoker/never smoker exposure ratios and linear extrapolation.

To a certain extent, differences among the various estimates are expected because each type of estimate (for example, linear extrapolation or population-attributable risk methods) requires different assumptions and all estimates are only crude approximations without confidence limits. However, even if the confidence limits for all estimates include all other estimates, this does not explain the 22- to 301-fold difference between the linear extrapolation estimate of 12 lung cancer deaths and the other estimates.

The previous discussion shows that the substantial difference between our estimates and the alternative estimates cannot be adequately explained by errors in our estimates of the number of never smokers, the average exposure for current and never smokers, or

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Table 9. Alternative estimates of the number of ETS-attributable never smoker lung cancer deaths (LCD) (both sexes combined) in 1980 in the U.S.

Method	Description	Estimated LCDs
Phenomenological	Repace and Lowrey's (1985) sex and age-specific difference in LCD rates between Seventh-Day-Adventist (SDA) and non-SDA never smokers is applied to the 1979/1980 National Health Interview Survey estimate of the U.S. population of never smokers by sex and age (Arundel *et al.*, 1986).	3,610
Linear Extrapolation Based on ETS Exposure	Repace and Lowrey's (1985) estimate of 555 nonsmoker (never and ex-smokers combined) LCDs is adjusted for the National Health Interview Survey estimate of the percentage (63.87%) of nonsmokers that are never smokers.	354
Linear Extrapolation Based on Cotinine Ratios	The estimated smoking-attributable LCD rate for current smokers of 284 LCD/100,000 men and 121 LCD/100,000 women is divided by the ratio of the weighted average urine cotinine level of 1483.7 ng/ml for smokers and 5.72 ng/ml for never smokers in four studies (Williams *et al.*, 1979; Kyerematen *et al.*, 1982; Jarvis *et al.*, 1984; Wald *et al.*, 1984).	265
Population Attributable Risk (PAR) Estimates*		
RR is 1.35	*RR* is Wald's *et al.*, (1986) estimate of the geometric mean risk observed in 13 epidemiological studies from six countries. The risk is 1.53 for never smokers living with smokers and 1.18 for never smokers not living with smokers, after adjustment for the misclassification of 7% of ever smokers as never smokers and a relative difference in ETS exposure of 3.0 (Wald & Ritchie, 1984) for the two groups of never smokers. p is 0.249 for male and 0.505 for female never smokers (see text). The average PAR is 0.21 for male and 0.26 for female never smokers.	1,852
RR is 1.14	*RR* is the geometric mean risk observed in 5 epidemiological studies from the U.S. only (NRC, 1986). The risk is 1.16 for never smokers living with a smoker and 1.05 for never smokers living with never smokers after adjustment for a misclassification rate of 6%, a risk for misclassified ever smokers of 2.0 and a threefold exposure difference for the two groups of never smokers. p is 0.249 for male and 0.505 for female never smokers. The average PAR is 0.072 for male and 0.094 for female never smokers.	655

*The adjusted PAR equation (Eq. 5, p. 292, NRC, 1986) equals:

$$\frac{p_1(RR_1-1)+(1-p_1)(RR_2-1)}{p_1(RR_1)+(1-p_1)(RR_2)}$$

where p_1 is the proportion of never smokers who live with an ever smoker, RR_1 is the risk for never smokers who live with an ever smoker and RR_2 is the risk for never smokers who live with never smokers. The PAR × N, the total number of never smoker LCDs in 1980 (3,479 male, 4,312 female (Table 8)), gives the estimated number of never smoker lung cancer deaths from ETS exposure. The estimates are calculated for each sex and then summed.

the lung cancer risk for current smokers. On the contrary, there is also evidence to indicate that the estimate of 12 lung cancer deaths is too high. The difference cannot be due to an error in the estimated number of never smokers because all estimates are based on the National Health Interview Survey estimate of the population of never smokers ≥ 35 years of age. There are two possible explanations for the difference: either the alternative estimates given in Table 9 overestimate the true risk, or there are major problems with one or more of the four major assumptions underlying the linear extrapolation estimate, which causes it to underestimate the true risk.

Alternative Estimates

Several features of the two alternative linear estimates indicate that they could overestimate the true risk. The estimate based on cotinine ratios assumes that cotinine levels in the blood or urine of smokers

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and nonsmokers measure comparable exposures. As discussed earlier, this assumption is probably not valid. Cotinine in smokers measures the lung's exposure to particulate tobacco smoke, whereas cotinine in nonsmokers measures nasal and pharyngeal exposure to the gas phase. Neither the site nor type of exposure is comparable. Repace and Lowrey's (1985) linear extrapolation estimate could also overestimate the true risk from ETS exposure because it appears to overestimate both the never smoker's average exposure and the average smoker's lung cancer risk. The method also uses the inhaled exposure instead of the retained exposure.

The alternative risk-based estimates depend on epidemiological estimates of the lung cancer risk from ETS exposure. The phenomenological estimate is based on a risk of 1.73 for male and 2.54 for female never smokers, calculated from the difference in lung cancer mortality rates for Seventh-Day-Adventist nonsmokers and another group of nonsmokers. The method assumes that the Seventh-Day-Adventists received less exposure to ETS than the other group of nonsmokers. However, the mortality rates for the Seventh-Day-Adventists are based on only 15 female and 10 male deaths. Consequently, these rates are unstable, with large fluctuations in the death rates instead of a consistent increase with each successive age group. These fluctuations could lead to an overestimate of the lung cancer risk from ETS exposure (Arundel *et al.*, 1986).

The population-attributable risk estimates are based on only three parameters: the geometric mean lung cancer risk from ETS exposure, the proportion of never smokers exposed to ETS, and the number of never smokers at risk. The difference between the population-attributable risk and linear estimates cannot be attributed to errors in the estimated value of the number of never smokers at risk because this parameter is also used in the linear estimate. Both methods also assume that all never smokers are exposed to ETS, though the population-attributable risk method calculates separate risks for the proportion of never smokers exposed to ETS at home and the proportion not exposed at home. These proportions are derived from the 1970 National Health Interview Survey estimate that 24.9% of male and 50.5% of female never smokers age 35 and over live with a current or former smoker.

The population-attributable risk method, based on a geometric mean risk of 1.35 from 13 epidemiological studies, estimates 1,852 lung cancer deaths in 1980 among never smokers from exposure to ETS. The method is similar to that used by Robins (1986). Robins' method estimates 1,807 lung cancer deaths in 1980 among never smokers of both sexes from ETS exposure.

The difference in the linear and population-attributable risk estimates could occur if all estimates of the geometric mean risk overestimate the true risk. Lee (1986) has shown that the misclassification of ever smokers as never smokers could result in an overestimate of the geometric mean risk. However, the population-attributable risk estimates are adjusted for misclassification, though the misclassification rate and the lung cancer risk for misclassified ever smokers is only crudely estimated. The geometric mean risk could also be biased by response or recall bias in the case-control studies on which it is based or by differences in the age distribution of lung cancer cases in the epidemiological studies and the age distribution of never smokers in the U.S. Furthermore, the geometric mean risk is a crude risk; it is not adjusted for age or any other possible or established risk factor for lung cancer such as occupation, socioeconomic status, or diet. The lack of adjustment for other risk factors could bias the geometric mean risk either upwards or downwards.

Assumptions of the Linear Estimate

Three of the four major assumptions of the linear extrapolation estimate can provide a plausible explanation of the difference between our estimate and the population-attributable risk estimates. The assumption of no low threshold, where the risk falls to zero, is irrelevant. The second assumption is that the dose-response relationship is linear. The difference between the estimates can be explained if the true dose-response relationship is nonlinear and convex, such that one unit of exposure at low doses is substantially more carcinogenic than one unit of exposure at high doses. However, most dose-response studies of chemical carcinogens have found sublinear or "hockey stick" shaped relationships between exposure and risk in which one unit of exposure at low doses results in a smaller increase in risk than one unit of exposure at high doses (Hoel *et al.*, 1983). The linear assumption is usually recommended as a conservative estimate of risk because it is believed to err towards overestimating the true risk (Anderson, 1983).

The best fitting equation for the lung cancer death rate per unit of exposure in a 1951–1971 cohort study of 34,440 British doctors is nonlinear and equal to $0.26\ (\text{dose}+6)^2$, where dose is the average number of British cigarettes smoked at the time of the study (Doll & Peto, 1978). This equation indicates that the linear assumption overestimates the risk from ETS exposure. For example, the sales-weighted average British cigarette between 1951 and 1971 delivered 29.9 mg of particulate tobacco smoke to the smoker (Wald *et al.*, 1981). An average inhaled exposure for male never smokers of 0.62 mg/day of particulate ETS (equivalent to 0.02 British cigarettes) results in an annual excess inhaled-exposure risk of 0.06 LCD/100,000 never

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Table 10. Relative particulate tobacco smoke exposure for current and never smokers in 1955, 1968 and 1980

	1955	1968	1980
Proportion of population that smoke[a]	0.376	0.386	0.345
Tobacco weight of an average cigarette (grams)[b]	1.12	0.95	0.80
Tar (including nicotine) delivery per cigarette (mg)[c]	40.1	23.1	14.2
Cigarettes/day (CPD) smoked by the average smoker[d]	26.2	29.7	29.3
Never smoker's exposure index[e]	11.0	10.9	8.1
Smoker's daily exposure (mg)[f]	1050.6	686.1	416.1
Ratio of smoker's exposure/never smoker's exposure index	95.5	62.9	51.4

[a]1955: ≥ age 18 (SG, 1979), 1968: ≥ 17 (SG, 1979), 1980: ≥ 17 (1979/1980 National Health Interview Survey).
[b](USDA, 1985).
[c]1955 and 1968 (SG, 1981), 1980 (Tobacco Inst., 1981).
[d]For 1955 and 1968, equals per capita (≥ 18) number of cigarettes sold (Table 1-1, NRC, 1986)/proportion of population who smoke/365. For 1980, equals the number of cigarettes sold/National Health Interview Survey estimate of the number of never smokers ≥ 17.
[e]Proportion of population that smoke × tobacco weight × CPD per smoker.
[f]Tar delivery per cigarette × CPD.

smokers. Adjusting for the retained exposure decreases the risk to 0.008 LCD/100,000, which predicts 1.4 lung cancer deaths among male never smokers compared to the linear estimate of 8 deaths. The same relative decline for female never smokers would estimate 0.9 female lung cancer deaths, for a combined minimum estimate of 2.3 lung cancer deaths in 1980.

The other two assumptions of the linear estimate (equal risk per unit of exposure for smokers and never smokers, and that all risk is attributable to particulate exposure) can be examined together. The difference between our estimate and the population-attributable risk estimates can be explained if ETS is substantially more carcinogenic per unit of exposure than mainstream smoke. The lowest alternative estimate of 265 lung cancer deaths requires ETS to be as much as 22 times more carcinogenic than mainstream smoke, the highest population-attributable risk estimate of 1,852 lung cancer deaths requires ETS to be as much as 154 times more carcinogenic, and the phenomenological estimate requires ETS to be as much as 301 times more carcinogenic. ETS could be more carcinogenic than mainstream smoke if there were substantial differences in the chemical composition, deposition pattern, or deposition site of passively inhaled sidestream smoke versus actively inhaled mainstream smoke.

The linear estimate is essentially based on a difference in exposure between never and current smokers, while the phenomenological and population-attributable risk estimates are based on a difference in risk between never smokers with and without regular exposure to ETS. Given the large difference in the exposure of never and current smokers, the relative risks of 2.54 and 1.73, on which the phenomenological model is based, or the relative risks of 1.34 or 1.14 used in the population-attributable risk estimates, are far too high. In our opinion, a substantially greater carcinogenicity for ETS versus mainstream smoke is the most plausible factor which could explain the large difference between our linear estimate and the risk-based estimates, assuming that the latter estimates more closely approximate the true risk. A supralinear relationship between exposure and risk could also explain the difference, though this appears less probable. Otherwise, the risk-based estimates must substantially overestimate the true risk. Further research on the relative carcinogenicity of mainstream and sidestream smoke and the dose-response relationship for low exposures to tobacco smoke is necessary.

Effect of Past Exposures

One final problem needs to be addressed. The use of the average particulate ETS exposure for never smokers in 1980 will underestimate the average never smoker's risk if the smoker/never smoker exposure ratio was less in the past than in 1980, and if past exposures are more important in the development of lung cancer than recent exposures. The latter condition may not be true: the lung cancer risk for ex-smokers declines with the number of years since smoking ceased (SG, 1979). The former condition can be examined by estimating the change in exposure over time. The average smoker's past exposure can be determined from the average cigarette consumption and the average particulate delivery. Though the average

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never smoker's past exposure cannot be estimated directly, it is possible to construct a relative exposure index from annual data on the average amount of tobacco in a cigarette, the percentage of the population that smokes, and the average cigarettes per day smoked per smoker.

Table 10 gives the average smoker's exposure as well as the average never smoker's exposure index for 1955, 1968, and 1980. The smoker's exposure has declined 60.4% since 1955 (mostly due to increased filter use), whereas the never smoker's exposure index has declined only 26.4%. The faster decline for smokers means that the 1980 smoker/never smoker exposure ratio is less than the ratio in 1955 (Table 10) and that the 1980 risk estimate for never smokers should overestimate the true risk based on a composite of past exposures.

The estimated average particulate ETS exposure for current smokers in 1980, based on machine-smoked particulate ETS deliveries, would overestimate the decline in the average smoker's exposure if each cigarette is smoked more intensely in 1980 than in 1955. However, the average smoker's exposure will decline faster than the never smoker's average exposure unless the average particulate ETS delivery/cigarette in 1980 is increased by 86% to 26.4 mg. An 86% average increase in the intensity with which each cigarette is smoked is unlikely; experimental studies of smokers given cigarettes with substantially lower tar and nicotine deliveries than their usual brand find the intensity of smoking to increase by 33% to 66% (Herning *et al.*, 1981; Ashton *et al.*, 1979).

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References

Adams, J. D., O'Mara-Adams, K. J., and Hoffman, D. (1985) On the mainstream-sidestream distribution of cigarette smoke components. Presented at the 39th Tobacco Chemists' Research Conference, Montreal, Canada. Cited by NRC, 1986.

Akiba, S., Blot, W. J., and Kato, H. (1986) Passive smoking and lung cancer among Japanese women. *Cancer Res* **46**, 4804–4807.

Altman, P. L. and Ditmer, D. S. (1971) *Respiration and circulation*. Federation of American Society for Experimental Biology, Bethesda, MD.

Anderson, E. L. and the Carcinogen Assessment Group of the U.S. Environmental Protection Agency. (1983) Quantitative approaches in use to assess cancer risk. *Risk Analysis* **3**, 277–295.

Arundel, A., Irwin, T., and Sterling, T. (1986) Nonsmoker lung cancer risks from tobacco smoke exposure: an evaluation of Repace and Lowrey's phenomenological model. *Environ. Sci. Health C4* **1**, 93–118.

Ashton, H., Stepey, R., and Thompson, J. W. (1979) Self-titration by cigarette smokers. *Br. Med. J.* **2**, 357–360.

Blake, C. L., Coffman, M. A., and Heywood, D. J. (1981) Indoor air quality problems in public buildings. Clayton Environmental Consultants, Inc., Marietta, GA.

Blot, W. J. and Fraumeni, J. F. (1986) Passive smoking and lung cancer. *J. Natl. Cancer Inst.* **77**, 993–1000.

Brownson, R. C., Reif, J. C., Keefe, T. J., Ferguson, S. W., and Pritzel, J. A. (1987) Risk factors for adenocarcinoma of the lung. *Am. J. Epidemiol.* **125**, 25–34.

Buffler, P. A., Pickle, L. W., Mason, T. J., and Contant, C. (1984) The causes of lung cancer in Texas, pp. 83–99. In M. Mizell and P. Correa, Eds. *Lung Cancer: Causes and Prevention*. Verlag-Chemie International Inc., New York, NY.

Chan, W. C. and Fung, S. C. (1982) Lung cancer in non-smokers in Hong Kong, pp. 199–202. In E. Grundmann, Ed. *Cancer Campaign, Vol. 6. Cancer Epidemiology*. Gustav Fischer Verlag, Stuttgart.

Chrostek, W. (1979) Town Center Associates Building, Rockville Maryland. Health Hazard Evaluation Determination Report HHE 79-77-605. National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Chrostek, W. J. and Moshell, A. N. (1982) General Telephone Company Building, York, PA. Health hazard evaluation report HETA 81-275-11. National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Cole, P. and MacMahon, B. (1971) Attributable risk percent in case-control studies. *Brit. J. Prev. Med.* **25**, 242–244.

Collett, C. (1985) Report on indoor air quality and ventilation measurements. Atrium One Building, Cincinnati, OH. Theodor D. Sterling Ltd., Vancouver, B.C., Canada.

Corn, M. (1974) Characteristics of tobacco sidestream smoke and factors influencing its concentration and distribution in occupied spaces. *Eur. J. Respir. Dis. (Suppl.)* **91**, 21–36.

Cornwell, R. J., Piacitelli, L., Kullman, G. Engelberg, A. L., Sorensen, W., and Simpson, J. (1981) Report on Health Services Administration Building. TA-81-007-985. Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Correa, P., Pickle, L. W., Fontham, E., Lin, Y., and Haenszel, W. (1983) Passive smoking and lung cancer. *Lancet* **2**, 595–597.

Cuddeback, J. E., Donovan, J. R., and Burg, W. E. (1976) Occupational aspects of passive smoking. *Am. Ind., Hyg. Assoc. J.* **37**, 263–267.

Dalager, N. A., Pickle, L. W., Mason, T. J., Correa, P., Fontham, E., Stemhagen, A., Buffler, P. A., Ziegler, R. G., and Fraumeni, J. F. (1986) The relation of passive smoking to lung cancer. *Cancer Res.* **46**, 4808–4811.

Dalhamn, T. (1968) Effect of different doses of tobacco smoke on ciliary activity in cat. Variations in amount of tobacco smoke, interval between cigarettes, content of "tar", nicotine and phenol. *J. Nat. Cancer Inst. Mono.* **28**, 79–87.

Davies, C. N., Heyder, J., and Ramu, M. C. S. (1972) Breathing of half-micron aerosols 1. *Experimental. J. Appl. Physiol.* **32**, 591–600.

Doll, R. and Peto, R. (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and nonsmokers. *J Epidemiol. Community Health* **32**, 303–312.

Elliot, I. P. and Rowe, D. R. (1975) Air quality during public gatherings. *J. Air Pollut. Control Assoc.* **25**, 635.

Enstrom, J. E. and Godley, F. H. (1980) Cancer mortality among a representative sample of nonsmokers in the U.S. during 1966–68. *J. Nat. Cancer Inst.* **65**, 1175–1183.

EPRI (Electric Power Research Institute) (1984) *Manual on indoor air quality*. Lawrence Berkeley Laboratories, Palo Alto, CA.

Eudy, L. W., Thone, F. A., Heavner, D. L., Green, C. R., and Ingebrethsen, B. J. (1986) Studies on the vapor-particulate phase distribution of environmental nicotine by selective trapping and detection methods. *Proceedings of the 79th Annual Meeting of the Air Pollution Control Association*. Air Pollution Control Association, New York, NY.

First, M. W. (1984) Environmental tobacco smoke measurements: retrospect and prospect. *Eur. J. Respir. Dis.* **5**(Suppl), 9–16.

Friedman, G. D., Petitti, D. B., and Bawol, R. D. (1983) Prevalence and correlates of passive smoking. *Am. J. Public Health* **73**, 401–405.

Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J. Nat. Cancer Inst.* **66**, 1061–1066.

2023381964

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

Garfinkel, L., Auerbach, O., and Joubert, L. (1985) Involuntary smoking and lung cancer: a case-control study. *J. Nat. Cancer Inst.* 75, 463–469.

Gillis, C. R., Hole, D. J., Hawthorne, V. M., and Boyle, P. (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur. J. Respir. Dis. (Suppl.)* 133, 121–126.

Gorman, R. (1980) Memo on Congressman Cavanaugh's office, Washington DC. Report TA 80-67-754, National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Gunter, B. J. and Thoburn, T. W. (1985) Memo on Denver Western Petroleum Corporation Offices, Denver Colorado. HETA 85-084, U.S. Dept Health and Human Services, Public Health Services, Region 8, Denver, CO.

Hammond, E. C. (1964) Smoking in relation to mortality and morbidity: Findings in first thirty-four months of a follow-up of a prospective study started in 1959. *J. Nat. Cancer Inst.* 32, 1161–1188.

Hammond, E. C. (1966) Smoking in relation to the death rates of one million men and women. *J. Nat. Cancer Inst. Mono.* 19, 127–204.

Hammond, E. C. and Seidman, H. (1980) Smoking and cancer in the United States. *Prev. Med.* 9, 169–173.

Hecht, S. S., Carmella, S., Morl, H., and Hoffman, D. (1981) A study of tobacco carcinogenesis XX. Role of catechol as a major cocarcinogen in the weakly acidic fraction of smoke condensate. *J. Nat. Cancer Inst.* 66, 163–168.

Herning, R. I., Jones, R. T., Bachman, J., and Mines, A. H. (1981) Puff volume increases when low-nicotine cigarettes are smoked. *Br. Med. J.* 283, 187–189.

Heyder, J. (1982) Particle transport onto human airway surfaces. *Eur. J. Resp. Dis. Suppl.* 63, 29–50.

Hicks, J. (1981a) Unidentified office building and manufacturing plant in Hayward, CA. Fireman's Fund Insurance Co., San Francisco, CA.

Hicks, J. D. (1981b) Tight building syndrome: Summary of a building in San Rafael, CA. Fireman's Fund Insurance Co, Sacramento, CA.

Hill, P. and Marquardt, H. (1980) Plasma and urine changes after smoking different brands of cigarettes. *Clin. Pharmacol. Ther.* 27, 652–658.

Hiller, F. C., McKusker, K. T., Mazumber, M. K., Wilson, J. D., and Bone, R. C. (1982) Deposition of sidestream cigarette smoke in the human respiratory tract. *Am. Rev. Respir. Dis.* 125, 406–408.

Hirayama, T. (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Br. Med. J.* 282, 183–185.

Hodgson, M. and Morley, P. (1983) Hubert H. Humphrey Building, Washington DC, Health Hazard Evaluation Report, HETA 82-169-1302, National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Hoegg, U. R. (1972) Cigarette smoke in close spaces. *Environ. Health Perspec.* 51, 117–128.

Hoel, D. G., Kaplan, N. L., and Anderson M. W. (1983) Implication of nonlinear kinetics on risk estimation in carcinogenesis. *Science* 219, 1032–1037.

Hoffmann, D., Schmeltz, I., Hecht, S. S., and Wynder, E. L. (1978) Tobacco carcinogenesis. In: Gelboin HV and Ts'o POP, eds. *Polycyclic hydrocarbons and cancer Vol. 1.* Academic Press, New York, NY.

Hosein, H. R. and Corey, P. (1986) Domestic air pollution and respiratory function in a group of housewives. *Can. J. Public Health* 77, 44–50.

Hollett, B. A. (1979) Federal Office Building #6, Washington, D.C. Hazard Evaluation and Technical Assistance Report TA 79-52, National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Humble, C. G., Samet, J. M., and Pathak, D. R. (1987) Marriage to a smoker and lung cancer risk. *Am. J. Public Health* 77, 598–602.

IARC (International Agency for Research on Cancer). (1985) Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Chemistry and Analysis of Tobacco Smoke. *World Health Organization* 38, 83–126.

Jarvis, M., Tunstall-Pedoe, H., Feyerabend, C., Vesey, C., and Salloojee, Y. (1984) Biochemical markers of smoke absorption and self reported exposure to passive smoking. *J. Epidem. Comm. Health* 38, 335–339.

Jarvis, M. J., Russell, M. A. H., Feyerabend, C., Eiser, J. R., Morgan, M., Gammage, P., and Gray, E. M. (1985) Passive exposure to tobacco smoke: saliva cotinine concentrations in a representative population sample of non-smoking schoolchildren. *Br. Med. J.* 291, 927–929.

Kabat, G. C. and Wynder, E. L. (1984) Lung cancer in nonsmokers. *Cancer* 53, 1214–1221.

Koo, L. C., Ho, J. H-C., and Lee, N. (1985) An analysis of some risk factors for lung cancer in Hong Kong. *Int. J. Cancer* 35, 149–155.

Kyerematen, G. A., Michael, M. S., Damiano, B. S., Dvorchik, B. H., and Vesell, E. S. (1982) Smoking-induced changes in nicotine disposition: Application of a new HPLC assay for nicotine and its metabolites. *Clin. Pharmacol. Ther.* 32, 769–780.

Lebowitz, M. D., Corman, G., O'Rourke, M. K., and Holberg, C. J. (1984) Indoor-outdoor air pollution, allergen and meteorological monitoring in an arid Southwest area. *J. Air Pollut. Control Assoc.* 34, 1035–1038.

Lee, P. N. (1986) Misclassification as a factor in passive smoking risk. *Lancet* 2, 867.

Lee, P. N., Chamberlain, J., and Alderson, M. R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Br. J. Cancer* 54, 97–105.

Lofroth, G. and Lazaridis, G. (1986) Environmental tobacco smoke: comparative characterization by mutagenicity assays of sidestream and mainstream cigarette smoke. *Environ. Mutagen.* 8, 693–704.

Lynch, C. J. (1984) Half-lives of selected tobacco smoke exposure markers. *Eur. J. Respir. Dis. (Suppl.)* 133, 63–67.

Maxwell, J. C. (1981) *Historical sales trends in the cigarette industry.* Lehman Brothers Kuhn Research, New York, NY.

Moschandreas, D. J., Zabransky, J., and Pelton, D. J. (1980) Indoor air quality characteristics of the office environment. Geomet Technologies Inc., Gaithersburg, MD.

Muir, C. F. (1974) Tobacco smoke inhalation. *Eur. J. Respir. Dis (Suppl.)* 91, 44–46.

NCHS (National Center for Health Statistics). (1970) Estimation and sampling variance in the Health Interview Survey. U.S. Department of Health and Human Services, Public Health Service, Health Services and Mental Health Administration, (PHS Pub. No. 1000-Series 2-No. 38), Hyattsville, MD.

NCHS (National Center for Health Statistics). (1981) Current estimates from the National Health Interview Survey: U.S. Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics and Technology, National Center for Health Statistics. (DHHS Publ No. (PHS) 81-1564) Hyattsville, MD.

NCHS (National Center for Health Statistics). (1986) Unpublished Vital Statistics. U.S. Department of Health and Human Services, Public Health Service. Division of Vital Statistics, Statistical Resources Branch, Hyattsville, MD.

Neal, A. D., Wadden, R. A., and Rosenberg, S. H. (1978) Evaluation of indoor particle concentrations in an urban hospital. *Am. Ind. Hyg. Assoc. J.* 39, 578–582.

NICSH (National Interagency Council on Smoking and Health). (1978) Smoking and the workplace: Business survey. National Interagency Council on Smoking and Health, New York, NY.

NRC (National Research Council). (1986) Committee on Passive Smoking, Board on Environmental Studies and Toxicology. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.* National Academy Press, Washington, D.C.

Parker, G. B., Lee, R. N., and Dennis, G. W. (1983) Monitoring Indoor Pollutants in Two Small Office Buildings to Support a Modeling Study. Pacific Northwest Laboratory, Battelle Memorial Institute, Richland, WA.

Pershagen, G., Hrubec, Z., and Svensson, C. (1987) Passive smoking and lung cancer in Swedish women. *Am. J. Epidemiol.* 125, 17–24.

Repace, J. L. and Lowrey, A. H. (1985) A quantitative estimate of nonsmokers lung cancer risk from passive smoking. *Environ. Int.* 11, 3–22.

2023381965

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Repace, J. L. and Lowrey, A. H. (1980) Indoor air pollution, tobacco smoke and public health. *Science* **208**, 464–472.

Robins, J. (1986) Risk assessment — exposure to environmental tobacco smoke and lung cancer, pp. 294–337. In: Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council, *Environmental Tobacco Smoke, Measuring Exposures and Assessing Health Effects*. National Academy Press, Washington, DC.

Rogot, E. and Murray, J. L. (1980) Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Rep.* **95**, 213–222.

Russell, M. A. H., Wilson, C., Patel, U. A., Feyerabend, C., and Cole, P. V. (1975) Plasma nicotine levels after smoking cigarettes with high, medium, and low nicotine yields. *Br. Med. J.* **2**, 414–416.

Salisbury, S. A. (1979) Midwest Stock Exchange. Chicago, IL. Health Hazard Evaluation and Technical Assistance Report TA 78-39, National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Salisbury, S. A., Roper, P., Miller, B., and Kelter, A. (1982) Marietta Tower, Atlanta, GA. Health Hazard Evaluation and Technical Assistance Report TA 80-122-1117, National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Sepkovic, D. W., Haley, N. J., and Hoffman, D. (1986) Elimination from the body of tobacco products by smokers and passive smokers. *J. Am. Med. Assoc.* **256**, 863.

Sexton, K., Spengler, J. D., and Treitman, R. D. (1984) Personal exposure to respirable particles: a case study in Waterbury, Vermont. *Atmos. Environ.* **18**, 1385–1398.

SG (Surgeon General) (1979) Smoking and Health. U.S. Department of Health and Human Services. Rockville, MD.

SG (Surgeon General) (1981) The Changing Cigarette. U.S. Department of Health and Human Services, Rockville, MD.

SG (Surgeon General) (1982) Smoking and Health. U.S. Department of Health and Human Services. Rockville, MD.

Spengler, J. D., Dockery, D. W., Turner, W. A., Wolfson, J. M., and Ferris, B. G. (1981) Long-term measurements of respirable sulfates and particles inside and outside homes. *Atmos. Environ.* **15**, 23–30.

Spengler, J. D., Treltman, R. D. Tosteson, T. D., Mage, D. T., and Soczek, M. L. (1985) Personal exposures to respirable particulates and implications for air pollution epidemiology. *Environ. Sci. Technol.* **19**, 700–707.

Sterling, E. M., Steeves, J. F., Wrigley, C. D., Sterling, T. D., and Weinkam, J. J. (1985) Building performance database. *Proceedings of the International Conference on Building Use and Safety Technology, March 12–14, 1985*. National Institute of Building Sciences, Los Angeles, CA.

Sterling, T. D., Collett, C. W., and Sterling, E. M. (1987) Environmental tobacco smoke and indoor air quality in modern office work environments. *J. Occup. Med.* **29**, 57–62.

Stober, W. (1984) Lung dynamics and uptake of smoke constituents by nonsmokers — a survey. *Prev. Med.* **13**, 589–601.

Szalai, A. (1972) ed. *The Use of Time*. Mouton Press, The Hague.

Tharr, D. G. (1980) Passaic City Hall, Passaic, NJ. Health Hazard Evaluation and Technical Assistance Report TA 80-71, National Institute for Occupational Safety and Health, National Technical Information Services, Springfield, VA.

Thompson, C. R., Hensel, E. G., and Kats, G. (1973) Outdoor-indoor levels of six air pollutants. *J. Air Pollut. Control Assoc.* **23**, 881–886.

Tobacco Institute (1981) U.S. tar/nicotine levels dropping. *The Tob. Observ.* **6**, 1.

Todd, G. F. (1978) Cigarette consumption per adult of each sex in various countries. *J. Epidemiol. Commun. Health* **32**: 289–293.

Trichopoulos, D., Kalandidi, A., and Sparros, L. (1983) Lung cancer and passive smoking: Conclusion of Greek study. *Lancet* **2**, 677–678.

Turiel, I., Hollowell, C. D., Miksch, R. R., Rudy, J. V., and Young, R. A. (1981) *The Effects of Reduced Ventilation on Indoor Air Quality in an Office Building*. Lawrence Berkeley Laboratories, Berkeley, CA.

USDA (U.S. Department of Agriculture) (1985) Tobacco: outlook and situation report. DOA Publ. No TS-129, U.S. Government Printing Office, Washington, D.C.

USDC (U.S. Department of Commerce) (1982). Bureau of the Census. Preliminary estimates of the population of the United States, by age, sex, and race: 1970 to 1981. Population estimates and projections series P-25, No. 917. Government Printing Office, Washington, D.C.

USDC (U.S. Department of Commerce) (1981) Statistical abstract of the United States. Government Printing Office, Washington, D.C.

Wald, N. J., Doll, R., and Copeland, G. (1981) Trends in tar, nicotine, and carbon monoxide yields of UK cigarettes manufactured since 1934. *Br. Med. J.* **282**, 763–765.

Wald, N. J., Boreham, J., Bailey, A., Ritchie, C., Haddow, J. E., and Knight, G. (1984) Urinary cotinine as marker of breathing other people's tobacco smoke. *Lancet* **1**, 230–231.

Wald, N. J., Nanchahal, K., Thompson, S. G., and Cuckle, H. S. (1986) Does breathing other people's tobacco smoke cause lung cancer? *Br. Med. J.* **293**, 1217–1222.

Wald, N. and Ritchie, C. (1984) Validation of studies on lung cancer in non-smokers married to smokers. *Lancet* **1**, 1067.

Weinkam, J. J. and Sterling, T. D. (1987) Changes in smoking characteristics by type of employment from 1970 to 1979/1980. *Am. J. Industr. Med.* **11**, 539–561.

Wigle, D. T., Collishaw, N. E., Kirkbride, J., and Mao, Y. (1987) Deaths in Canada from lung cancer due to involuntary smoking. *Can. Med. Assoc. J.* **136**, 945–951.

Williams, C. L., Eng, A., Botvin, G. J., Hill, P., and Wynder, E. L. (1979) Validation of students' self-reported cigarette smoking status with plasma cotinine levels. *Am. J. Public Health* **69**, 1272–1274.

Wynder, E. L. and Hoffman, D. (1967) *Tobacco and tobacco smoke*. Academic Press, New York, NY.

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Appendix: Equations and Parameters of the Linear Extrapolation Estimate

Never Smoker's Retained Particulate ETS Exposure:

$$\text{Exp N} = \text{NRR}(\text{ExpH} + \text{ExpR} + \text{ExpW} + \text{ExpO})$$

where:

$$\text{Home Exposure (ExpH)} = \text{R} \times \text{LH} \times \text{PH} \times \text{AH}$$

$$\text{Restaurant/Bar Exposure (ExpR)} = \text{R} \times \text{LR} \times \text{PR} \times \text{AR}$$

$$\text{Work Exposure (ExpW)} = \text{R} \times \text{LXW}(\text{PWW} \times \text{AWW} + \text{PBW} \times \text{ABW} + \text{PRW} \times \text{ARW})$$

$$\text{Other Exposure (ExpO)} = \text{R} \times \text{LO} \times \text{PO} \times \text{AO}$$

R = the respiration rate, Lx = the length of exposure in each location x, Px = the proportion of never smokers exposed to particulate ETS in each location x, Ax = the ambient particulate ETS level in each location x, WW = white-collar workplace, BW = blue-collar workplace, NRR = the never smoker particulate ETS retention rate.

Smoker's Retained Particulate Tobacco Smoke Exposure:

$$\text{ExpSM} = \text{SMRR}(\text{CPD} \times \text{TAR})$$

SMRR = the smoker particulate tobacco smoke retention rate, CPD = the average number of cigarettes smoked/day/smoker, TAR = the average tar delivery/cigarette.

Smoker's Lung Cancer Death (LCD) Rate:

$$\text{SMLCDR} = 100{,}000(\text{NSMLCD}/\text{SMPOP})$$

where:

$$\text{NSMLCD} = \text{TLCD} - \text{LCDN} - \text{LCDEX} - \text{LCDSM}$$

NSMLCD = the number of smoking-attributable LCDs among current smokers, SMPOP = the total number of current smokers, TLCD = the total number of LCDs in1980, LCDN = number of LCDs which occurred among never smokers, LCDEX = number of LCDs which occurred among ex-smokers, LCDSM = number of LCDs which occurred among smokers from nonsmoking causes.

where:

$$\text{LCDEX} = (\text{TLCD} - \text{LCDN})/(1 + \text{NCS}/\text{NES} \times 2.26)$$

where:

NCS = the number of current smokers, NES = the number of ex-smokers.

Never Smoker's LCD Rate:

$$\text{NLCDR} = \text{SMLCDR}/(\text{ExpSM}/\text{ExpN})$$

SMLCDR = the LCD rate per 100,000 smokers, ExpSM = average smoker's particulate tobacco smoke exposure, ExpN = average never smoker's particulate ETS exposure.

Number of Never Smoker Lung Cancer Deaths from ETS Exposure:

$$= (\text{NPOP}/100{,}000)\text{NLCDR}$$

NPOP = number of never smokers, NLCDR = the lung cancer death rate per 100,000 never smokers.

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THE POTENTIAL ASSOCIATION OF LUNG CANCER WITH PASSIVE SMOKING

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The potential association of lung cancer with passive smoking has been studied epidemiologically, clinically, and with mathematical models. There have been both positive and negative studies, such that the association is still considered a potential rather than probable one. These studies, and the mathematical models, indicate that major factor in determining the relationship is the dose, and that more research is required to determine the dose side of the dose-response relationship.

Introduction

There has been a growing interest in the potential of passive (or involuntary) smoking as cause of lung cancer (Lebowitz and Apostolides, 1982). This concern is based on chemical analysis of sidestream and mainstream smoke, experiments on the effects of tobacco smoke constituents *in vitro* and *in vivo*, and some recent epidemiological evidence which may link involuntary smoking in spouses to lung cancer mortality. Since the average person spends the great majority of time indoors, it is assumed that there is a large potential for exposure to tobacco smoke generated by others (NRC, 1981).

Exposure Factors

Of the various chemicals derived from tobacco smoke, four of great concern are polycyclic aromatic matter (POM) expressed as benzo(*a*)pyrene (BaP), dimethylnitrosamines, dimethyl benz-anthracene (DMBA) and alpha-emitting radionuclides, mostly polonium 210. Comparisons of mainstream and sidestream smoke have been made by several authors (Brunneman and Hoffman, 1978; Rylander, 1974, 1984; Schmeltz *et al.*, 1975; U.S. Surgeon General, 1980). Further, at least some POM originates from other indoor sources, such as food cooking, wood burning, and other combustions (NRC, 1981). Radiation dosage does occur from cigarettes (Martell, 1974; Little *et al.*, 1965; Radford and Hunt, 1964; DiFranza and Winters, 1982); its relative contribution, to that from other sources, is still debatable (Martell, 1983; Jacobi, 1984). It has been difficult to determine the potential effects of nitrosamines or the radon progeny in the normal indoor environment on humans (Bergman and Axelson, 1983; Martel, 1983).

In vitro studies (Medical Perspectives, 1984; NRC, 1972) have shown some increased mutagenic activity of tobacco products. Studies in mice have shown that condensate from the cigarette end has tumor-producting activity greater than that leaving the mouth piece of the cigarette (U.S. Surgeon General, 1982; Wynder and Hoffman, 1967). Other experiments have been reported to show combined effects of air pollution extracts and cigarette smoke condensate when installed in or on tissue in large amounts (Hoegg, 1972). Sister chromated exchange in cultured human lymphocytes is induced by cigarette smoke condensate, though not appreciably by BaP (Hopkin, 1984).

Passive inhalation of cigarette smoke can produce tracheobronchial epithelial dysplasia and metaplasia in animals at high concentrations of smoke (Holland *et al.*, 1963; U.S. Surgeon General, 1982). The relevance to humans can be questioned because of these high levels, at excess of levels encountered by humans (Schmeltz *et al.*, 1975). "''Attempts to induce significant numbers of bronchogenic carcinoma in laboratory animals were negative in spite of major efforts with several species and strains" (U.S. Surgeon General, 1982). Furthermore, human exposure experiments with sidestream smoke in unventilated rooms

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showed that air concentrations of vapor phase and particulate phase substances decreased with their presence, and the exposure of nonsmokers to tobacco smoke under realistic conditions does not appear to produce inhalation of sufficient amounts of tobacco smoke components traditionally (Holland *et al.*, 1963; Hugod *et al.*, 1978). Hiller *et al.* (1982) measured the deposition fraction of environmental tobacco smoke in humans; the mean was 11% (the median was 8%).

Only mathematical models, such as that of Repace and Lowrey (1985), appear to estimate dosage to humans from environmental tobacco smoke that may be carcinogenic. These models are based on mathematical assumptions and calculations that appear to include overestimations (Esmen, 1981). The dose so derived does not reflect estimates based on actual controlled laboratory studies (First, 1984; Hiller *et al.*, 1982; Hinds *et al.* 1983; Jarvis and Russell, 1984; Johnson and Letzel, 1984; Schievelbein and Richter, 1984), as summarized recently by Hiller (1984), and evaluated by a WHO Committee (1983). Actual estimates (First, 1984; Hiller *et al.* 1982, 1985; Hinds *et al.*, 1983; Jarvis and Russell, 1984; Johnson and Letzel, 1984; Schievelbein and Richter, 1984) imply a dosage to the passive smoker of less than 2 (range of 0.1–2) cigarettes/day, except in unusual circumstances; these estimates are ten- to one-hundred-fold less than that in the Repace and Lowrey model (1985). Dosage is the key ingredient to the question of association, and it will require further determination.

Epidemiology

Some have opined that involuntary cigarette smoke possibly contributes to the otherwise unexplained phenomena of lung cancer in nonsmokers and differences in lung cancer rates between rural and urban areas (Cooper *et al.* 1968; Hoegg, 1972), though most studies and reviews link this mortality to occupational and other environmental exposures (Cooper *et al.* 1968; Goldsmith and Friberg, 1977; Lippmann and Schlesinger, 1979; Shy *et al.*, 1978; U.S. Surgeon General, 1982).

At least in the United States, lung cancer deaths in nonsmokers have not increased in the last three decades in either sex (Garfinkel, 1981). Studies of the relationship between involuntary smoking and lung cancer have been performed primarily in females who are exposed to the sidestream smoke of their spouses. Females have lower lung cancer rates than males, even in smokers, and the relative risk ratios appear lower for female smokers than male smokers; these differences are thought to be due to differences in age of onset of smoking, of smoking habits, and occupational exposures (U.S. Surgeon General, 1980, p. 114). Although the occupational exposure of women along with their smoking may produce similar rates to those of males under similar circumstances, fewer women have such exposures (U.S. Surgeon General, 1980, p. 179). In general population samples, however, it is more difficult to accurately ascertain smoking and other exposures in women, especially in traditional societies.

Prospective Population Studies

In a recent study in Japan (Hirayama, 1981), nonsmoking wives of smoking husbands were claimed to have a higher risk of dying from lung cancer than nonsmoking wives of nonsmoking husbands. This study followed 91,540 nonsmoking wives age 40 and older for 14 yr (1966–1979). Husband's age (40–59, 60+) or occupation (agriculture or other) were used to standardize mortality rates for lung cancer and were compared depending on the smoking habits of the husbands; standardization was not on the wives ages or occupations. A relative risk ratio of 2 (1.90–2.36) in nonsmoking wives of heavy smoking husbands was found and was considered significant by the Mantel-extension chi two tailed test; it has not been resolved whether the statistical test was performed correctly. A re-analysis of the data (Harris and DuMouchel, 1981) used a chi-square test statistic for the disaggregated data. Estimating relative risk using maximum likelihood methods for the total set of data also yielded significantly higher rates in the nonsmoking wives with smoking husbands. However, in evaluating the disagregated data several inconsistencies and/or differences of small magnitude were found. For instance, for wives of husbands age 40–59 who work elsewhere, the rates for the nonsmoking husband group (10.0) and the rates for the ex- or light-smoking husbands (11.2) are not different; for husbands age 60 or more who work in agriculture, the rates for women with heavy-smoking husbands (35.7) are less than the rates for women with ex- or light-smoking husbands (43.8). As with wives of husbands age 40–59 who work elsewhere, wives whose husbands are age 60 or older who work elsewhere who are ex- or light-smokers have rates not distinguishably different from the wives of nonsmoking husbands of that age group or occupational group.

Further problems exist in evaluating the Japanese data, predominantly relating to the actual estimate of exposure to tobacco smoke and of other exposures in females. It may be difficult to correctly ascertain smoking habits of females in this traditional society, as smoking is considered improper for women. Furthermore, indoor exposures to indoor combustion products, especially charcoal or kerosene burning, is likely in Japanese society, and is probably greater in rural females.

Other exposures, either occupational, perri-occupational, ambient, and/or socially related are likely to have clouded the true differences amongst these women (Dore, 1967; Embree, 1939; Vogel, 1971). One Japanese study reported increased cancer related to heating and cooking fuels used especially in rural

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areas, as did one Chinese study (Leung, 1977); another Chinese study found no such effect (MacLennan *et al.*, 1977). It is difficult to ascertain how much time each group of women spends with their smoking or nonsmoking husbands. It is also difficult to determine the effects of ventilation in these homes on the exposure level; it may be that the women in the agriculture areas have homes with more ventilation as well as infiltration of pesticides and other substances. These problems persist because of other determinants of exposure, determinants of socioeconomic status, and the urban rural differences have not been characterized sufficiently, despite assumptions made about such differences (Hammond and Selikoff, 1981; Hirayama, 1981). Further, the major differences seen in wives of husbands age 40 to 59 in agriculture was based on only 3 female deaths in wives of nonsmoking husbands; further estimates of risk, depending on one's assumptions, could lead to different results (Rutsch, 1981).

Finally, other smoking-related causes of death were not significantly different between passive and nonpassive smoking wives. Subsequent letters to the editor of the *British Medical Journal* have been contradictory. Dosage estimates, as shown by the 1984 International Workshop, have been incorrect.

One study in the United States has been analyzed to determine the possible influence of husbands smoking on the mortality experience of nonsmoking wives (Garfinkel, 1981). Adjusted lung cancer deaths among women with nonsmoking husbands matched with women with smoking husbands were not significantly higher in the first group than in the latter groups. The adjusted relative risk ratio for wives with husbands who smoked a pack or more per day was only 1.04. There is no serious disease in the women at the onset of this study. The relationship between the death certificate cause of death and that in the medical records in females was only 83%, indicating possible biases in this study and in other studies of mortality; this bias may be greater for females, as the death certificates and medical records match more closely for males. Only 41% of husbands' smoking was at home. The fact that mortality ratios for light smokers compared to nonsmokers is nearly 5 to 1 in the United States compared to 2 to 1 in Japan would indicate that one would be more likely to see the effects of involuntary smoking in the United States. However, it appears unlikely the wives with husbands who smoke heavily can have mortality ratios that approach those of regular cigarette smokers (Garfinkel, 1984). Thus, the Japanese study (and Greek study, below) may have possible biases in selection or in measurement (Garfinkel, 1984; Rylander, 1984). Garfinkel reported (1984) that their autopsy studies have indicated no atypical cells in the 47 nonsmokers studies. They are starting a new chohort study of 1.2 million people, in which more accurate exposure information will be obtained (Garfinkel, 1984).

Knoth *et al.* (1984) studied 59 females with bronchogenic carcinoma in Germany. The proportion who were nonsmoking spouses of smokers (61.5%) indicated a risk 3 times that based on smoking males. This indicates that there is a high likelihood of misclassification/bias in this study.

Gillis *et al.* (1984) have preliminary results from a cohort study of 16,000 in 2 urban communities in West Scotland. It was shown that cancer incidence and mortality may inconsistently be associated with some small but nonsignificant increase in risk in nonsmoking female spouses of smoking husbands.

There is a major problem in the phenomenological use of data on epidemiological Seventh Day Adventists (SDAs) in mathematical models (Repace and Lowrey, 1985). Generalizations based on SDAs are unjustified as they are a distinctly different group of individuals (compared to a random sample of the general population); they have different lifestyles in addition to different smoking habits. Epidemiologically, Repace and Lowrey (1985) use insufficient methods to control for differences in age and other confounding factors (Friedman *et al.*, 1983; Garfinkel, 1984; Roth, 1981; WHO, 1982; WHO/EURO, 1983).

As Rylander has indicated (1984), none of the cohort studies were designed to study this relationship. In fact, Friedman *et al.* (1983) showed the high rates of misclassification of smoking by spouses, which would over-estimate risk. Garfinkel (1984) has confirmed this misclassification bias. It is difficult to obtain complete information on passive smoking in nonsmoking women. An epidemiological study has to be designed specifically to measure their exposure as accurately as possible, and this is difficult to do. Furthermore, the long-term effects of passive smoking is difficult to establish because of the problems in classification and because of other exposures and/or previous exposures (such as in previously married women); marriage to a smoker is not equivalent to exposure, and other factors may mask important differences.

Case-Control Studies

Case-control studies are meant to measure relative risk (not true probability) and generate hypotheses (not definitive results).

Garfinkel (1984) reported on a recent attempt to do a case-control study. He indicated that half of the primary lung cancer cases were misdiagnosed (by histology) and half of the nonsmokers were current or ex-smokers by their own report (Garfinkel, 1984). When this study was completed (Garfinkel *et al.* 1985), they had 134 cases, 90 with home exposure. Their relative risk ratio by the number of cigarettes the husband smoked in the home was 1.31 overall and over 2.0 for

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more than 1 pack per day, both significant. Both are lower than that for light smokers.

Another case-control study (Sandler *et al.*, 1985) found no significant increase in lung cancer risk but found increases in non-tobacco-related cancers, that is, those normally used as positive controls for reasons of internal reliability and validity (i.e., the study is considered unreliable if the positive control shows an association and invalid if it is significant but the cases—lung cancer—are not). Other methodological and ascertainment problems might explain the gaffe.

A case-control study in Greece (Trichopoulos *et al.* 1981) compared spouses' smoking habits of female lung cancer patients with spouses' smoking habits of other female patients, after excluding smoking females. As indicated by the authors, having only 39 married nonsmoking females in the lung cancer group did not enable them to draw strong conclusions about their odd ratios. Furthermore, only about one-fourth of the lung cancer cases had histological conformation. The controls were matched on their occupation, age, education level, urban/rural residence, and duration of marriage, but were not matched on residence (*vis-à-vis* ambient exposures), other exposures, husband's occupation, or other factors of indoor exposure. It was noted that among the original set of female cases and female controls that the female cases smoked more, as expected, but the relative risk ratio of smoking cases appeared similar to the relative risk ratio of the nonsmoking married females with smoking spouses. These ratios were corrected in subsequent publications (Heller, 1983; Trichopoulos, 1984). Again the ascertainment bias of smoking in females in a somewhat traditional society is possible. The personal habits of the various groups of women are unknown, although others (Hammond and Selikoff, 1981) believe that they are such as to make the estimates of the differences conservative.

Other factors that would affect the exposure to the husband's smoking, such as ventilation in the home, and the time spent with the husband, is unavailable. Since this was a case control study with limited information about co-linear variables or intervening variables, it would take a prospective study in the community with better data collection to insure a better estimate of the probability of risk. Furthermore, such a study would avoid observer bias produced by using only one physician and the need to only one control group (Hammond and Selikoff, 1981). With a prospective study, there is a possibility of better histological conformation, including inclusion of adenocarcinomas which the investigators presently excluded; more recent investigations indicate that all four major histological types, including adenocarcinoma, are related to cigarette smoking (U.S. Surgeon General, 1980, p. 113).

Chan and Fung (1982) have reported on a hispital-based case-control study in Hong Kong. Comparing 83 female lung cancer cased to 139 females controls showed no difference in the proportions of each group with smoking husbands. Koo *et al.* (1985) performed a case control study in Hong Kong, in which the analysis of all histological types in never-smoking females did not reveal any significant increase in relative risk from passive smoking. Other environmental factors which encourage bronchial irritation are suspected. They found histological typing responsible for misclassification and biased risk values between active and passive smoking seen in other studies.

Correo *et al.* (1983) published a case-control study of lung cancer in nonsmoking men and women classified by the number of cigarettes smoked per day by their spouses. Relative risks in women was significant only for those with heavy (40+/day) smoking husbands. However, this study was based on 22 lung cancers in nonsmoking women and 8 in nonsmoking men. They examined whether or not there was an association with parents' smoking habit when they were children as well. No association was found with paternal smoking. There was an elevated risk in smokers whose mothers smoked, after controlling for other variables, but no elevated risk in nonsmokers. No attempts were made to ascertain *post hoc* bias in reporting, nor accuracy of the estimate of exposure.

Kabat and Wynder (1984) reported on 25 nonsmoking men and 53 nonsmoking women classified not only by whether or not their spouse smoked, but also whether or not they were exposed to smoke of others at work or at home. In women there was no increase in risk of lung cancer for any of these three measures. In men there was increased risk of lung cancer in those exposed at work (barely statistically significant), but no increase in risk in those exposed at home or from spouse's smoking. They concluded that more data must be collected before any conclusion can be drawn relating to the effects of passive smoking.

A study based on interviewing the next of kin of deceased cases (Miller, 1984) showed slightly higher rates of all cancer deaths in women with smoking husbands (versus those with nonsmoking husbands) but lower rates of coronary artery disease and other causes in those same women. The odds ratio was calculated incorrectly. Nevertheless, it showed significantly increased cancer deaths in only one of 4 age groups, and as low as 0.4 in another age group; the overall odds ratio was not significant. Examining only nonemployed wives reduced the significant odds ratio to nonsignificance ($X^2 = 0.93$), although the overall ratio was now significant; the latter still requires age adjustment before considered suggestive. Employed wives had an overall odd ratio of 0.8.

Models

Since estimated exposure in passive smokers is between 0.01 – 2 cigarette/day, one could linearily estimate an age adjusted relative cancer risk between

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1.03–1.36. The impact of this on cancer incidence especially in the majority of the range, is considered small (Vutuc, 1983). The difficulty is that we do not know if the dose-response curve is linear (no threshold) or nonlinear (with a threshold), indicating that extrapolation at these low levels of exposure is risky.

The one-hit model of cancer risk is a crude model; it assumes a non-threshold linear dose-response relationship and extrapolation to low doses. As shown by others (Roth, 1981; Albert, 1981; Althshuler, 1981; Caplan *et al.*, 1983; Jacobi, 1984; Luken and Miller, 1977; Radford and St. Clair, 1984; Schnerderman, 1981; Task Force, 1982; Wyzga, 1981), this model overestimates risk from more likely exponential or mulihit models. The model and methods used by Repace and Lowrey (1985) and others do not provide estimates of precision, confidence intervals, or consistency estimates (Beran, 1971; Black, 1970; Luken and Miller, 1977; Smith, 1961), the very statistical bases of estimation procedures.

Discussion

The fundamental dilemmas are (1) basic epidemiological or statistical errors in previous studies which are often ignored by nonepidemiologists (U.S. Surgeon General, 1982, 1984); (2) misclassification of exposure and of lung cancer (Friedman *et al.*, 1983; Garfinkel, 1984); and (3) the problem of dose (Albert, 1983) and exposure-response relationships (Jarvis and Russell, 1984). The biological consequences of smoking require a certain dose over a certain time (Garfinkel, 1984; IARC, 1984; Vutuc, 1984), which if low, may not even be significantly noticed in low doses in large populations (U.S. Surgeon General, 1982). It seems unlikely that passive smoking is responsible for about one-third of the annual lung cancer mortality among U.S. nonsmokers (Repace and Lowrey, 1985). One must recognize also that nonsmokers may have developed lung cancer from other environmental agents: radon progency may account for 5%–30% (most likely 5%–15%) of such mortality (Edling *et al.*, 1984; Hess *et al.*, 1983; Jacobi, 1984; Radford and St. Clair, 1984), and volatile organic compounds (Albert, 1983; NRC, 1972), asbestos (Hirayama, 1981; Holland *et al.*, 1963), and various other environmental factors have been blamed as well. In conclusion, the Repace and Lowrey (1985) estimates of nonsmokers' lung cancer risk from passive smoking is an overstatement.

Lung cancer risk estimated to be twice as high in passive smokers as in nonsmokers not exposed to the smoke of their partner is hardly conceivable because of the absence of cell modifications in the tracheobronchial tract of passive smokers (Garfinkel, 1984). Thus, the problem of passive smoking may be too small to measure in population studies (Garfinkel, 1981; Rylander, 1984). A 1983 International workgroup (Rylander, 1984) agreed that there was sufficient association to support further research. Further case-referent approaches could be considered. Further research should measure actual exposure to environmental tobacco smoke, as recently requested by NCI (NCI RFA 84-Ca-14). It should consider the contributions of specific agents thought to produce cancer, such as nitrosamines and polycyclic hydrocarbons. Further research should include other possible carcinogenic agents and confounding factors, such as occupational exposure, other exposures of the nonsmoking household members, social status and other risk variables.

Conclusion

One must weigh several factors before we claim certain causality that smoking by parents, spouses, friends, and workmates will definitely give nonsmokers cancer. As previous public health experience has shown when one lacks causal links, anxiety increases, as do its sequaelae, as does cost, with increasing iatrogenic disease (i.e., induced by the ""healer") and little benefit in actually preventing overt disease, disability and premature mortality. However, once causality has been shown, we must act quickly to prevent disease. In the interim, we should work to prevent active smoking.

The U.S. Surgeon General's report 1982 (p. 249) stated: ""Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem." At present, it can only be concluded that it will require further investigation before the estimated probability of risk can be determined.

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References

Albert, R. (1981) The uses of risk assessment in regulatory issues, in ""Conference proceedings: Environmental risk assessment," R. J. Hock, ed., EPRI EA2064 2.1-14. EPRI, Palo Alto, CA.

Albert, R. E. (1983) Discussion: Toxic substances in the atmosphere environment, *J. Am. Pollut. Control Assoc.* 836–837.

Althshuler, V. (1981) Modeling of dose response relationships, *Environ. Health Persp.* **42**, 23–27.

Beran, E. J. (1971) On distribution-free statistical inference with upper and lower probabilities, *Ann. Math. Stat.* **42**, 157–168.

Bergman, H. and Axelson, O. (1983) Passive smoking and indoor radon daughter concentrations, *Lancet* **2**, 1308–1309.

Black, M. (1970) *Margins of Precision*. Cornell University Press, Ithaca, NY.

Brunnemann, K. D. and Hofmann, D. (1978) Chemical studies on tobacco smoke. LIX. Analysis of volatile nitrosamines in tobacco smoke and polluted indoor environments, in Environmental Aspects of *N*-Nitroso Compounds, F. A. Walker, M. Castegnaro, L. Griciute and R. E. Lyle, eds., pp. 343–356. IARC Scientific Publication no. 19, International Agency for Research on Cancer, Lyon, France.

Caplan, R. J. *et al.* (1983) A generalized effective exposure modeling

2023391973

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program for assessing dose-response in epidemiologic investigations, *Comput. Biomed. Res.* **16**, 587–96.
Chan, W. C. and Fung, S. C. (1982) Lung cancer in non smokers in Hong Kong. in *Cancer Campaign: Geographical Pathology in Cancer Epidemiology*, E. Grundmann, ed., vol. 6, pp. 199–202. G. Fischer Verlag, Stuttgart.
Cheung, C. W. (1982) Figures from Hong Kong, *Munchener Medizin. Wochenschrift* **124**, 16 (in German).
Cooper, D. A., Crane, A. R. and Boucot, K. R. (1968) Primary carcinoma of the lung in nonsmokers, *Arch. Environ. Health* **16**, 398–400.
Correo, P. *et al.* (1983) Passive smoking and lung cancer, *Lancet* **2**, 595–597.
DiFranza, J. R. and Winters, T. H. (1982) Radioactivity in cigarette smoke, *New Engl. J. Med.* **307**, 310–313.
Dore, R. P. (1967) *City Life in Japan*. University of California Press, Berkeley, CA.
Edling, C. *et al.* (1984) Radon daughter exposure in dwelling and lung cancer, in *Indoor Air*, B. Berglund *et al.*, eds., vol. 2, pp. 29–34. Liber A. B. Tryck, Stockholm.
Embree, J. S. (1939) *Suye-Mura*. University of Chicago Press, Chicago.
Enterline, P. (1983) Cancer produced by non-occupational asbestos exposure in the U.S., *J. Am. Pollut. Control Assoc.* **33**, 318–22.
Enterline, P. (1983) Epidemiologic basis for the asbestos standard, *Environ. Health Persp.* **52**, 93–97.
Esmen, N. A. (1981) Limitation on dose estimation, *Environ. Health Persp.* **42**, 3–7.
First, M. W. (1984) Environmental tobacco smoke measurements: Retrospect and prospect, *Eur. J. Respir. Dis.* **65** Suppl. 133, 9–16.
Friedman, G. D. *et al.* (1983) Prevalence and correlates of passive smoking, *Am. J. Public Health* **73**, 401–405.
Garfinkel, L. (1981a) Let us not be diverted from the real problem, *Munchener Medizin. Wochenschrift* **123**, 1438–1483.
Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking, *J. Nat. Cancer Inst.* **66**, 1061–1066.
Garfinkel, L. (1984) Passive smoking and cancer—a prospective study, *Prev. Med.* **13**, 691–697.
Garfinkel, L., Aurback, O. and Joubert, L. (1985) Involuntary smoking and lung cancer: A case-control study, *J. Nat. Cancer Inst.* **75**, 463–469.
Gillis, C. R., Hole, D. J., Hawthorne, V. M. and Boyle, P. (1984) The effect of environmental tobacco smoke in two urban communities in the West of Scotland, *Eur. J. Respir. Dis.* **65** Suppl. 133, 121–126.
Goldsmith, J. R. and Friberg, L. T. (1977) Effects of air pollution on human health, in *Air Pollution*, 3rd ed., A. C. Stern, ed., vol. 2.
Gori, G. B. (1976) Low-risk cigarettes: A prescription, *Science* **194**, 1243–1246.
Gori, G. B. and Lynch, C. J. (1978) Toward less hazardous cigarettes, *J. Am. Med. Assoc.* **240**, 1255–1259.
Hammond and Selikoff (1981) Passive smoking and lung cancer with comments on two new papers, *Environ. Res.* **24**, 444–452.
Harris, J. E. and DuMouchel, W. H. (1981) Letter to the editor, *Brit. Med. J.* **283**, 915.
Heller, D. (1983) Passive smoking and lung cancer, *Lancet* **2**, 1309.
Hess, C. T., Weiffenbach, C. V., and Norton, S. A. (1983) Environmental radon and cancer correlation in Maine, *Health Phys.* **45**, 339–348.
Hiller, F. C., McCusker, K. T., Mazumber, M. K., Wilson, J. D. and Bone, R. C. (1982) Deposition of sidestream cigarette smoke in the human respiratory tract, *Am. Rev. Respir. Dis.* **125**, 406–408.
Hiller, F. C. (1984) Intake of smoke constituents by nonsmokers—experimental evidence, *Prev. Med.* **13**, 602–607.
Hinds, W. *et al.* (1983) A method for measuring respiratory deposition of cigarette exposure during smoking, *Am. Ind. Hyg. Assoc.* **44**, 113–118.
Hirayama, T. (1981) Nonsmoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan, *Brit. Med. J.* **282**, 183–185.
Hoegg, U. R. (1972) Cigarette smoke in closed spaces, *Environ. Health Persp.* 117–128.
Holland, R. H., Kozlowski, E. J. and Booker, L. (1963) The effects of cigarette smoke on the respiratory system of the rabbit. A final report, *Cancer* **16**, 612–615.
Hopkin, J. M. (1984) Sister chromatid exchange induction by cigarette smoke, *Basic Life Sci.* **29** Pt B, 927–937.
Hugod, C., Hawkins, L. H. and Astryp, P. (1978) Exposure of passive smokers to tobacco smoke constituents, *Int. Arch. Occup. Environ. Health* **42**, 21–29.
Jacobi, W. (1984) Expected lung cancer risk from radon daughter exposure in dwellings, in *Indoor Air*, B. Berglund *et al.*, eds., vol. 1, pp. 31–42. SBRC/Liber A. B. Tryck, Stockholm.
Jarvis, M. J. and Russell, M. A. H. (1984) Measurement and estimation of smoke dosage to non-smokers from environmental tobacco smoke, *Eur. J. Respir. Dis.* **65**, Suppl. 133, 68–75.
Johnson, L. C. and Letzel, H. (1984) Measuring passive smoking: Methods, problems, and perspectives, *Prev. Med.* **13**, 705–716.
Kabat, G. C. and Wynder, E. L. (1984) Lung cancer in nonsmokers, *Cancer* **53**, 1214–1221.
Knoth, A., Bohn, H. and Schmidt, F. (1984) Passive smoking as a causal factor of bronchial carcinoma in female nonsmokers, *Medizin. Klinik* **78**, 66–69.
Koo, L. C., Ho, J. H. and Lee, N. (1985) An analysis of some risk factors for lung cancer in Hong Kong, *Int. J. Cancer* **35**, 149–155.
Lebowitz, M. D. and Apostolides, A. Y. (1982) Involuntary smoking and lung cancer, in The Health Consequences of Smoking: Cancer. A report of the Surgeon General. Publ. No. DHHS(PHS)82-50179; Section IV. U.S. Department of Health and Human Services, Washington, DC.
Leung, J. S. M. (1977) Cigarette smoking, the kerosene stove and lung cancer in Hong Kong, *Brit. J. Dis. Chest* **71**, 273.
Lippmann, M. and Schlesinger, R. B. (1979) *Chemical Contaminants in the Human Environment*. Oxford University Press, New York, NY.
Little, J. B., Radford, E. P. Jr., McCombs, H. L., and Hunt, V. R. (1965) Distribution of Polonium-210 in pulmonary tissues of cigarette smokers, *New Engl. J. Med.* **273**, 1343–1351.
Luken, R. H. and Miller, S. G. (1977) The benefits and costs of regulating benzene, *J. Am. Pollut. Control Assoc.* **31**, 1254–1259.
MacLennan, R., Da Costa, J., Day, N. E., Law, C. H., Kg, Y. K. and Shanmugaratnam, K. (1977) Risk factors for lung cancer in Singapore Chinese: A population with high female incidence rates, *Int. J. Cancer* **20**, 854–860.
Martell, E. A. (1974) Radioactivity of tobacco trichomes and insoluble cigarette smoke particles, *Nature* **249**, 215–217.
Martell, E. A. (1983) β-Radiation dose at bronchial bifurcations of smokers from indoor exposure to radon progency, *Proc. Nat. Acad. Sci. U.S.A.* **80**, 1285–1289.
Medical Perspectives on Passive Smoking. An International Symposium, Austria (1984) *Prev. Med.* **13**.
Miller, G. H. (1984) Cancer. Passive smoking and nonemployed and employed wives, *West. J. Med.* **140**, 632–635.
National Research Council (1972) *Particulate Polycyclic Organic Matter*, pp. 172–236, 245–246. National Academy Press, Washington, DC.
National Research Council (1981) *Indoor Pollutants* National Academy Press, Washington, DC.
National Research Council (1984) *Asbestos-form Fibers: Non-occupational Health Risk*. National Academy Press, Washington, DC.
Radford, E. P. Jr., and Hunt, V. R. (1964) Polonium-210, a volatile radioelement in cigarettes, *Science* **143**, 247–149.
Radford, E. P. and St. Clair, R. K. G. (1984) Applications of studies of miners to radon problems in homes, in *Indoor Air*, B. Berglund *et al.*, eds., vol. 2, pp. 93–96. SCBR/Liber A. B. Tryck, Stockholm.
Repace, J. L. and Lowrey, A. H. (1985) A quantitative estimate of nonsmokers' lung cancer risk from passive smoking, *Environ. Int.* **11**, 3–22.
Roth, H. D. (1981) Data quality and analysis in risk assessment, in Conference Proceedings: Environmental risk assessment, R. J. Hock, ed., pp. 65–76. EPRI EA2064 2.1-14. EPRI, Palo Alto, CA.
Rutsch, M. (1981) Letter to the editor: Nonsmoking wives of heavy smokers have a higher risk of lung cancer, *Brit. Med. J.* **282**, 985.
Rylander, R. (1984) Environmental tobacco smoke; Effects and exposure levels: Proceedings of a Workshop, *Eur. J. Respir. Dis.* **65**, Suppl. 133.
Rylander, R. (1974) Environmental tobacco smoke effects on the nonsmoker: Report from a Workshop, University of Geneva, *Scand. J. Respir. Dis.* **91**, Suppl.

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Sandler, D. P., Everson, R. B. and Wilcox, A. J. (1985) Passive smoking in adulthood and cancer risk, *Am. J. Epidemiol.* **121**, 37–45.

Schievelbein, H. and Richter, F. (1984) Influence of passive smoking on the cardiovascular system—A survey, *Prev. Med.* **13**, 626–644.

Schmeltz, I., Hoffman, D. and Wyner, E. L. (1975) The influence of tobacco smoke on indoor atmospheres, *Prev. Med.* **4**, 66–82.

Schnerderman, M. A. (1981) Extrapolation from incomplete data to total or lifetime risks at low doses, *Environ. Health. Persp.* **42**, 33–38.

Shy, C., Goldsmith, J., Hackney, J., Lebowitz, M. D. and Menzel, D. (1978) *Health Effects of Air Pollution*, American Thoracic Society, New York, NY.

Smith, C. A. B. (1961) Consistency in statistical inference and decision, *J. Roy. Stat. Soc.* Ser. B **23**, 1–37.

Task Force on Environmental Cancer and Heart and Lung Disease (1982) Fifth Annual Report to Congress, August, pp. 61–97.

Trichopoulos, D., Kalandidi, A., Sparros, L. and MacMahon, B. (1981) Lung cancer and passive smoking, *Int. J. Cancer* **27**, 1–4.

Trichopoulos, D. (1984) Passive smoking and lung cancer, *Lancet* **1**, 684.

U.S. Surgeon General (1979) Smoking and health. U.S. DHEW (PHS), U.S. Government Printing Office, Washington, DC.

U.S. Surgeon General (1980) The health consequences of smoking for women. U.S. DHEW, PHS, Office of the Assistant Secretary for Health, Office on Smoking and Health, Washington, DC.

U.S. Surgeon General (1982) The Health Consequences of Smoking: Cancer. USPHS, Washington, DC.

U.S. Surgeon General (1984) The Health Consequences of Smoking: Chronic Respiratory Diseases. USPHS, Washington, DC.

Vogel, E. F. (1971) *Japan's New Middle Class*. University of California Press, Berkeley, CA.

Vutuc, C. (1983) Lung cancer risk and passive smoking: Quantitative aspect, *Zentralbl. Bakteriol. Mikrobiol. Hyg.* **177**, 90–95.

Vutuc, C. (1985) Quantitave aspece of passive smoking and cancer, *Prev. Med.* **13**, 698–704.

World Health Organization (1982) Estimating human exposure to air pollutants. WHO, Geneva.

WHO/EURO. (1983) Indoor air pollutants: Exposure and health effects assessment, World Health Organization, Copenhagen.

Wynder, E. L. and Hoffman, D. (1967) *Tobacco and Tobacco Smoke*, pp. 183, 291. Academic Press, New York, NY.

Wyzga, R. (1981) Quantitative risk assessment: Concerns and research needs, in Conference Proceedings: Environmental Risk Assessment, R. J. Hock, ed., pp. 105–115. EA 2064, EPRI, Palo Alto, CA.

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LETTER TO THE EDITORS

Clark Johnson
Heinz Letzel, Munich, Germany

(Received 1 July 1985)

Dear Sir:

The article "A quantitative estimate of nonsmokers' lung cancer risk from passive smoking" by Repace and Lowrey (1985) concludes that 5,000 nonsmokers aged 35 yr or greater die every year in the United States of lung cancer as a result of exposure to tobacco smoke through passive inhalation. They model the exposure in two microenvironments: at home and at work. In an effort to determine the limitations of the methodology, we have re-examined their methods for estimating the exposure in the home. This seems to be justified, since they use the same strategy for both environments. This strategy can be summarized as follows:

1. Calculate the number of cigarettes smoked in the environment.
2. Use a theoretical model to translate this into a burden (uptake of particulate matter in mg per day).
3. Calculate the probability that a nonsmoker will receive this exposure.

Weaknesses on all three levels will be illustrated in this communication.

Inflated Estimate of Per-Person Cigarette Consumption

In paragraph 2 of Appendix A2 the authors assume that the average habitual smoker smokes 32 cigarettes/day. This rather high estimate of daily consumption was apparently abstracted from Repace and Lowrey (1980) in which they obtained a smoking rate per smoker-waking h of 2 cigarettes.

Hence, 32 cigarettes per day is calculated from an average rate of 2 cigarettes/h and 16 waking h/day. We prefer the estimate given in the 1980 National Health Interview: Survey Smoking Supplement of 21.7 cigarettes/day. If one corrects not only for this inflated estimate of cigarette consumption per day, but also for the incorrectly calculated percentages derived from Table A1 (33.75, 46.25, and 78.12% instead of 34.4, 45.9, and 81%, respectively), it can be calculated that 14.0 cigarettes are smoked by the average woman in the home, while 7.3 are smoked by the average man.

Inflated Estimates of Exposure

In the next paragraph the authors derive an estimate of the number of cigarettes smoked in the average U.S. home. Drawing on statistics generated by Bonham and Wilson (1981), they correctly indicate that 62% of U.S. homes *with children* contain one or more smokers and subsequently infer that of these homes (i.e., homes with smokers) 40% have two smokers, while in 33.5% the husband smokes, and 26.5% the wife smokes. Using these figures and the total number of cigarettes smoked at home as a basis, they calculate that 22 cigarettes/day are "estimated to be smoked daily in the average U.S. home." This estimate, if it is valid at all, can only be applied to homes with children, where one or more smokers are present. This can, by no means, be regarded as the average U.S. home. Using our baseline smoking rate the value is 14.6.

They subsequently assume that everyone of these cigarettes exposes a nonsmoking adult. This assumption implies that the housewife is always accompanied, and that, in the case where both husband and wife smoke, a third adult lives in the home. This assumption is by no means a conservative one.

It seems, however, that a method could be devised by which a more realistic estimate of household exposure in cigarettes per day could be calculated. If, for example, one attempts to calculate the number of cigarettes smoked in the home, which have the poten-

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tial of exposing a second adult, one is led to the following calculation

$$0.40 \times 0 + 0.265 \times 7.3 + 0.335 \times 7.3 = 4.4$$

40% of the homes, containing at least one smoker, contain in fact two smokers. These adults cannot be regarded as being primarily exposed through one another's smoking habit (i.e., 0.40×0). Similarly, if only one adult smokes, then the only time that their smoking can expose the other adult is at those points in time when they are both occupying the house. Hence, the 33.75% of the waking day spent in the home by the man is the limiting factor. We calculate that 7.3 cigarettes are consumed in these 5.4 h (i.e., 0.265×7.3 for women, 0.335×7.3 for men). Only 4.4 (30%) of the 14.6 cigarettes smoked at home can reasonably be attributed to exposure of nonsmoking adults.

Doubtful Theoretical Model not Clearly Applicable

The authors culminate their derivation by estimating the average exposure to particulate matter in mg/day for an adult nonsmoker. The equation used was originally published by the authors in 1980 (Repace and Lowrey, 1980).

In that article it is clear that the derivation of this formula depends upon two important simplifications of the smoking process:

1. Smoking as a statistical process.

In deriving the model, the authors assume "that smoking is a random process when it occurs among large groups." The authors, however, use the model in situations in which only a single smoker is present (i.e., the home), hardly one that can be regarded as characteristic of large group phenomenon.

2. Pollution equivalent to steady state levels.

A single smoker in a small room may produce a relatively constant level of pollution. The authors, however, assume that this constant level is equivalent to a theoretically derived "steady state", an assumption that has not been substantiated.

The application of this formula may be appropriate. However, it is incumbent upon the authors to offer the reader a demonstration of the fact that the assumptions, upon which it is based, can be massively violated without loss of validity.

Questionable Choices With Regard to Application of the Formula

Even if the equation is theoretically correct, which we doubt, it is incorrectly applied. As stated earlier, there is simply no basis to assume that an adult nonsmoker will be exposed for every hour of the waking day in every home where cigarette smoking takes place. Consequently, the authors' assumption that, if an adult is exposed, he or she will be exposed 16 h every day, is a dramatic inflation of an already inflated estimating procedure. From our calculations, a value of 5.4 h would more likely be appropriate.

Finally, the authors suggest that the probability of exposure is 62% for an adult nonsmoker. As reported earlier, this does not seem to be a correct estimate. Not only does it fail to account for the possibility that there are single parents, but it also includes as exposed those homes in which both parents smoke. Since we have no data for the percentage of single parents in the U.S. population, we will assume that this effect balances the number of times that a third adult actually is present in the home, where both parents smoke. Still, since 38% of the surveyed homes had no smokers, and 25% had two or more smokers, it seems far more reasonable to assume that the probability of exposure is 37% (100% − 38% − 25%).

Conclusion

Our examination has shown that the figures derived by the authors are based upon incorrect theoretical assumptions and inflated empirical estimates. The other calculations, contained in their paper, suggest to us that the tendency to choose inflated estimates with regard to exposure in the home was consistantly followed. As a result, one must conclude that the estimate of 5,000 lung cancer deaths per year in the United States, due to exposure to ambient tobacco smoke, does not represent an accurate assessment of the problem.

References

Bonham, G. S. and Wilson, R. W. (1981) Children's health in families with cigarette smokers, *Am. J. Publ. Health* 71, 290–293.

Repace, J. L. and Lowrey, A. H. (1980) Indoor air pollution, tobacco smoke, and public health, *Science* 208, 464–472.

Repace, J. L. and Lowrey, A. H. (1985) A quantitative estimate of nonsmokers' lung cancer risk from passive smoking, *Environ. Int.* 11, 3–22.

U.S. Surgeon General (1983) The health consequences of smoking-cardiovascular disease: A report of the Surgeon General. U.S. Department of Health, Education and Welfare, Public Health Service, Office of Smoking and Health, Washington, DC.

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HEALTH RISKS OF PASSIVE SMOKING: PROBLEMS OF INTERPRETATION

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Introduction

It is notoriously difficult to draw sound conclusions about causation from epidemiologic studies of associations. In his *Principles of Medical Statistics*, Sir Austin Bradford Hill, one of the founders of modern epidemiology, warns in connexion with positive associations: "Merely to presume that the relationship is one of cause and effect is fatally easy; to secure satisfactory proof or disproof, if it be possible at all, is often a task of very great complexity" (Hill, 1949).

The fundamental difficulty in conventional case-control and prospective surveys relates to the comparability of cases and controls. Thus, when we compare the incidence of lung cancer in smokers with that in nonsmoking controls we determine an association which, in the great majority of studies (U.S. Surgeon General, 1982), has been found to be positive. But, as we have been told *ad nauseam*, "association does not necessarily imply causation." Smokers and nonsmokers are generally self-selected and we need to be assured of the strict comparability of the two groups—in every pertinent respect except smoking—before inferring causation from association (Fisher, 1959; Yerushalmy, 1971). An analogous issue arises in connexion with various studies of passive smoking (Burch, 1981a): are persons married to smokers comparable, on the average, in all other pertinent respects to persons married to nonsmokers? Alas, the phenomenon of assortative mating is well established and accordingly we are not at liberty to assume that studies of any disease, in relation to the smoking status of the spouse or other household members, comply with the scientific requirements for valid inferences about cause. The nonsmoker who marries a smoker is unlikely to be representative of all nonsmokers.

My main purpose here is to examine Repace and Lowrey's (1985) arguments about lung cancer from the methodologic viewpoint.

Outline of Repace and Lowrey's Procedure

1. Exposure of nonsmokers

From measurements of the concentration of respirable particles between 0.01 and 3.0 μm diameter in representative samples of room air, and from surveys of lifestyles, Repace and Lowrey (1985) estimate the total exposures of nonsmokers (range and average) in terms of mg cigarette tar per day.

2. Epidemiologic studies of lung cancer in passive smokers

They review 13 epidemiologic studies of lung cancer risk in the nonsmoking spouses of cigarette smokers. In 12 of these, the only index of exposure was the strength of the spouse's smoking habit. The mortality ratio for persons married to smoking spouses versus those married to nonsmokers, clusters around a value of 2.0.

They also compare the sex- and age-adjusted mortality from lung cancer in Seventh Day Adventists (SDA) self-reported nonsmokers with that in never-smokers in the general U.S. population. Non-SDA never-smokers had an average standardized death rate from lung cancer that was 2.4 times that of SDA never-smokers. This latter group, they believe, was less likely to be exposed to ambient tobacco smoke than the former.

3. Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of passive smoking

Repace and Lowrey (1985) assume that the mortality ratio (2.4) derived from the SDA study implies causation and thereby calculate that some 4,700 lung cancer deaths per year have been caused among U.S. nonsmokers owing to passive smoking. They conclude that this figure agrees well (within 10%) with

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Hirayama's (1981) estimate of mortality from lung cancer attributable to passive smoking by the nonsmoking wives of Japanese smokers.

4. Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of active smokers

From many studies of lung cancer in active cigarette smokers reviewed by the U.S. Surgeon General (1982), and a linear exposure-response relationship, Repace and Lowrey derive an alternative estimate of the lung cancer death rate in the U.S. resulting from passive smoking. This procedure leads to an estimated 555 lung cancer deaths per year, nearly one order of magnitude lower than the rate (4700 per year) calculated under procedure 3 above.

5. Discussion of discrepancy between procedures 3 and 4

Repace and Lowrey speculate upon ways in which the lower estimate might be raised to the upper value.

Critique

Each of the above stages in Repace and Lowrey's procedure is discussed in turn.

1. Comment on: Exposure of nonsmokers

To make a valid estimate of the effective exposure of passive smokers to carcinogens we require the following information at least: (i) the nature of the carcinogens and their concentration in sidestream smoke particles; (ii) the anatomical location of the target cells; (iii) appropriate parameters of exposure such as the time-concentration and/or integral dose of carcinogens at the cells at risk; and (iv) an established model of tobacco smoke carcinogenesis incorporating factors for the sex- and age-dependence, dose and dose-rate effects, genetic susceptibility, etc..

Having little or no definitive guidance under any of these requirements, current estimates of effective exposure to carcinogens should be regarded as conjectural. Nevertheless, for the purpose of comparing passive smoking with active smoking, we have at present little option but to use the kind of data given in Repace and Lowrey's Table 1, although, according to Jarvis and Russell (1984), measurements of cotinine concentrations in urine samples are preferable.

2. Comment on: Epidemiologic studies of lung cancer in passive smokers

In addition to problems concerning occupational hazards, the choice of controls, etc., the reviewed epidemiologic studies are vulnerable to one elementary as well as a fundamental objection. To take the elementary objection first, Repace and Lowrey's Table 1 gives an estimated average daily exposure of nonsmokers in the home only, of 0.10 mg, and at work only, of 0.44 mg. It follows that studies of cancer and lung cancer risk in passive (or active) smokers, in relation to the smoking status of the spouse and household members, provide wholly inadequate evidence for association with actual exposure. Average total exposure appears from Repace and Lowrey's calculations to be dominated by the workplace component. This view is borne out in the Japanese environment by actual measurements of cotinine concentrations in urine samples from 167 male and 305 female nonsmokers (Matsukura *et al.*, 1984). Using Duncan's multiple-range test for several comparisons the authors found no significant difference between persons (200) not exposed at home, who had an average concentration of 0.51 $\pm$0.09 μg/mg creatinine, and those (272) exposed at home who had an average of 0.79 $\pm$0.10 μg/mg creatinine. Consequently, the relatively large differences in cancer risk between persons with smoking spouses, and those with nonsmoking spouses, are most unlikely to be due to differences in the levels of passive smoking, which on the average are small.

Only one study, that of Kabat and Wynder (1984), took account of exposure of nonsmokers in the workplace. That survey disclosed 6 male cases and 5 controls exposed in the home but 18 (out of 25) cases and 11 (out of 25) controls exposed at work ($P = 0.05$, ignoring the problem of multiple tests). With respect to women, Kabat and Wynder (1984) report: ". . . 16 of 53 cases were exposed at home compared to 17 of 53 controls, and 26 of 53 cases were exposed at work compared to 31 of 53 controls." Thus no significant differences were found in the data for women but the trend favours a prophylactic rather than a causal hypothesis.

The fundamental objection to all the reviewed studies of passive smoking concerns, of course, the lack of established comparability between the exposed and the nonexposed groups. This objection applies equally to studies of cancer risk in relation to the spouse's and household smoking, and to the comparison between SDA and non-SDA never-smokers. Seventh Day Adventists differ from never-smokers in the general U.S. population with respect to various features of lifestyle. Moreover, they are not drawn randomly from the general population; they are either self-selected and/or born of self-selected parents.

Hence, no reliable inferences about cause can be drawn from associations determined from either of the above types of evidence. In the absence of randomization we can have no confidence that hidden variables, particularly of a constitutional character, are not responsible for the observed associations.

By an interesting irony one of the studies of passive smoking (Sandler, *et al.*, 1985a, 1985b), if taken at face value, provides a fair refutation of the hypothesis

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that the association with the risk of cancer is causal (Burch, 1985). Sandler *et al.* (1985a) studied the overall cancer risk in active and nonsmokers in relation to the number of household members who smoke. The odds ratio was normalized to unity for households with no (other) members who smoked. For households with one (other) smoking member the odds ratios are 1.42 for active smokers and 1.45 for nonsmokers; for households with two (other) smokers the corresponding ratios are 2.25 and 2.32; and for three or more, the ratios are 2.42 and 2.75. Within the error limits the ratios for active smokers are identical with those for nonsmokers. Treating them as identical, Burch demonstrated that if A represents the carcinogenic effect of active smoking and P the carcinogenic effect of passive smoking resulting from one household smoker then, for either additive or multiplicative (interactive) models of carcinogenesis, $A + P = 0$ (Burch, 1985). This relation has three possible solutions: (i) active and passive smoking are both noncarcinogenic ($A = P = 0$); (ii) active smoking is carcinogenic and passive smoking is prophylactic ($A = -P$); and (iii) active smoking is prophylactic and passive smoking is carcinogenic ($P = -A$). Burch added: "The statistical uncertainty in Sandler's Table 1 is large enough to permit slightly less paradoxical inferences . . ."

Sandler *et al.* (1985b) replied to this analysis giving a further breakdown of their data showing odds ratios for the overall cancer risk in active and in nonsmokers in relation to household exposure to cigarette smoke during childhood only, adulthood only, and both periods of life. These supplementary data only deepen the paradox: Consider the simple additive model and define N as the average risk per person of cancer from all causes unconnected with smoking; A is the average additional risk from active smoking, including the smoker's exposure to the associated ambient cigarette smoke; P_c is the additional average risk from exposure to household cigarette smoke during childhood only; and P_A is the corresponding risk from exposure to household cigarette smoke during adulthood only. (The study population was aged from 15 to 59 yr and I assume these risks are substantially less than unity.) For nonsmokers exposed to household cigarette smoke during childhood only, with total risk $N + P_c$, we require from the Table of Sandler *et al.* (1985b): $(N + P_c)/N \cong$ the odds ratio, 1.3, giving $P_c \cong 0.3N$, a nonparadoxical result. For active smokers who were exposed to household cigarette smoke during childhood only, we have: $(N + A + P_c)/(N + A) \cong 1.9$. Substituting for P_c, we obtain $A \cong -0.7N$, a highly paradoxical result implying that active smoking in conjunction with passive exposure to household cigarette smoke during childhood only, is markedly prophylactic! A similar conclusion emerges from the multiplicative model.

However, when we consider the odds ratios for exposure to household cigarette smoke during adulthood only, we obtain $A \cong 3N$, which for the overall cancer risk in both sexes is substantially larger than directly observed associations (U.S. Surgeon General, 1982). Furthermore, although it is logically acceptable that active smoking in conjunction with passive smoking during childhood only is prophylactic, but in conjunction with passive smoking during adulthood only it is carcinogenic, the sharp reversal of effect between childhood and adult phases imposes a severe strain on biological models of carcinogenesis.

The "solution" to these findings of Sandler *et al.* (1985a, 1985b) that minimises paradox is, in effect, the original one: $A = P_c = P_A = 0$; with the odds ratios being attributed to selection effects arising from assortative mating.

3. Comment on: Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of passive smoking

Even if we adopt the hypothesis that passive smoking causes lung cancer and ignore selection problems, the evaluation of the epidemiologic studies for the purpose of risk calculations still poses severe problems. We have no direct measure of the relevant exposure to ambient cigarette smoke in any of the studies of associations. Although it is plausible to suppose that SDA nonsmokers have a lower exposure to ambient cigarette smoke than non-SDA never-smokers, we have no direct measure of the average levels in either group.

For these reasons alone the calculation by Repace and Lowrey of the number of lung cancer deaths (LCDs) per year in the United States caused by passive smoking must be regarded with the utmost suspicion. Associations determined from conventional case-control or prospective nonrandomized surveys should play no part in a scientific estimate of the magnitude of risks.

4. Comment on: Estimated death-rates from lung cancer in nonsmokers using epidemiologic studies

From the Surgeon General's estimate that 85% of all lung cancers are due to smoking and a linear exposure-response relation, Repace and Lowrey calculate that about 555 LCDs are caused in the United States each year through nonsmokers being exposed to ambient tobacco smoke. Elsewhere I have reviewed the methods used in the U.S. Surgeon General's (1982) report on cancer and, in particular, the arguments about lung cancer (Burch, 1983). If Lilienfeld's (1983) invited response to my many criticisms may be regarded as the best available defence of the Surgeon General's methods then I hope that I might be forgiven for suggesting that we need give little credence to them (Burch, 1984).

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To quote from my summary (Burch 1983): "Part II of the [Surgeon General's] Report describes the five criteria for causality that have guided the judgment of committees since 1964. I show that not one of the criteria, plausibly interpreted, is satisfied by the epidemiologic evidence for lung cancer." Lilienfeld (1983) was unable to demonstrate the contrary and to all my pointed enquiries he did not supply a single answer. On the Surgeon General's own criteria the hypothesis that the association between smoking and lung cancer is entirely causal in origin should be rejected.

My main attack, however, was launched at a more fundamental level: "The five criteria and the subjective method of 'judgment' are inappropriate to a scientific analysis; they should be replaced by the objective testing of hypotheses." Given a genuine association between a habit, *H*, such as cigarette smoking, and a cancer, *C*, such as lung cancer, we are obliged to consider all the following possibilities: (i) *H*, or something closely connected with it, such as the means of ignition, causes *C*; (ii) *C*, or a connected pre-*C* condition, causes *H* (I call this the "converse causal" hypothesis); (iii) a "third" factor causes, or predisposes to, both *H* and *C*; and (iv) because (i) to (iii) are not mutually exclusive any combination of them might be needed to account for an established association.

A comprehensive evaluation of an association requires an assessment of the relative contributions of (i), (ii) and (iii) complete with confidence limits. I had to admit: "My own attempts to derive the magnitude of the causal component of the association between smoking and lung cancer have been unsuccessful; errors of diagnosis and death-certification alone are apt to defeat such efforts." We are fortunate that other investigations—see below—help us to arrive at a "best estimate" of this causal component.

5. Comment on: Discussion of discrepancy between procedures 3 and 4

On encountering a near order of magnitude discrepancy between alternative estimates, most investigators would express dismay; it is to the credit of Repace and Lowrey that they display no outward signs of disappointment. Nevertheless, their ". . . discussion of alternative exposure-response relationships" has one conspicuous feature. Means are sought only to raise the lower estimate of 555 LCDs per year to the higher (4700 LCDs per year) and none in the reverse direction. I suggest that as little faith should be vested in the one estimate as in the other; both incorporate the same fundamental fallacy of arguing from association to causation.

It is widely, one hopes universally, recognized that the best way of eliminating most forms of bias, both in therapeutic trials and in epidemiologic studies of causation, is through randomization. Feinstein (1985) describes the randomized trial as the definitive "gold" standard in epidemiology. In the only practical form of such trials so far exploited in connection with the effects of active smoking, persons satisfying defined entry criteria were allocated randomly to one of two groups: (a) the intervention group which was subjected to intensive advice on the part of the investigators to quit smoking; or (b) the usual care, control group, which received no such advice. Levels of smoking were then monitored in both groups and after a suitable period the outcome, mainly in terms of mortality from various diseases and all causes, was assessed for the two groups.

Two such randomized trials have been carried out in which the findings for lung cancer have been reported: the Whitehall Study in London, England (Rose *et al.*, 1982) with a 10-yr follow-up; and the Multiple Risk Factor Intervention Trial (MRFIT, 1982) in the United States with a 7-yr follow-up. Although this latter trial cost some $120 million and, aiming at a reduction of heart disease, included dietary advice and stepped care treatment for hypertension in the intervention group—as well as antismoking advice—the results have not achieved prominence in the medical literature. They are not even mentioned by Repace and Lowrey. It is remarkable that reputable trials that cost so much should be valued so little.

Substantial reductions in smoking were achieved through the efforts of the investigators in the intervention groups, over and above the unplanned reductions in the usual care, control groups. By combining deaths and registrations for lung cancer in the Whitehall Study with deaths from lung cancer in the MRFIT (registrations not being reported in that study) we maximize numbers and obtain the best available direct epidemiologic test of the efficacy of reducing or quitting cigarette smoking. In the combined intervention, low-smoking groups, some 56 cases of lung cancer were recorded out of 7,142 men at entry (0.78%); in the usual care, relatively high-smoking groups, 53 cases were found out of 7,169 at entry (0.74%). The small advantage enjoyed by the high-smoking groups is, of course, not statistically significant; but it is strikingly consistent with the hypothesis that the association of active smoking with lung cancer has little or no causal component.

Because Sandler *et al.* (1985a, 1985b) studied all types of cancer, the outcome of the randomized trials for all cancers other than lung cancer are also of special interest. Some 88 cases (1.23%) were recorded in the combined low-smoking intervention groups but only 60 cases (0.84%) in the more heavily smoking usual care groups! It would be interesting to know whether a detailed statistical analysis of these combined results would reject the null hypothesis, as it did in the Whitehall Study at the level $P = 0.003$ (Rose *et al.*, 1982).

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One possible weakness of this type of intervention trial must be mentioned. Quitting smoking might be followed by psychological stress, or other changes in lifestyle, that are carcinogenic. Rose *et al.* (1982) observed only "minor" psychological effects of intervention but believe that further study is needed to test the hypothesis that quitting smoking has adverse effects on the cancer risk.

Before concluding the review of these randomized trials the findings for deaths from all causes should be quoted because they yield the largest numbers and have some claim to be the most important. In the combined intervention groups, 388 deaths in 7,142 were reported (5.43%); and in the more heavily smoking control groups, 388 deaths in 7,169, or 5.41%, were reported. (It should be remembered that in the MRFIT study the intervention group also received dietary advice and treatment for hypertension.) Suffice it to say that a reduction in overall mortality does not appear to be among the benefits of quitting smoking.

This is not an isolated finding; it corroborates an earlier analysis (Burch, 1981b) that was also designed to defeat the bias of self-selection and was exempt from the problems connected with intensive intervention. To avoid the errors of certification of the cause of death I analysed the temporal trends in sex- and age-specific mortality from all causes in England and Wales, over the period 1950 to 1976. These trends were compared, for various latent periods, with the corresponding temporal trends in sex- and age-specific rates of cigarette consumption (on a "constant tar" basis), which rose during the early part of the period surveyed and fell during the latter part. The fall in death rates was greater during the rise in cigarette consumption than during its fall. Differences in the age-pattern of mortality between the early and late periods showed that, up to the age of about 45 yr, the fall in overall mortality was almost entirely accounted for by the near eradication of tuberculosis. No causal effects of smoking on overall mortality could be discerned although, if the associations observed in case-control and prospective studies had a causal basis, they should have been readily detected.

Conclusions

When the most reputable of direct epidemiologic studies, randomized controlled intervention trials, fail to demonstrate any of the benefits widely expected from quitting active smoking, it is not surprising that Repace and Lowrey's alternative estimates of the effects of passive smoking on the incidence of lung cancer—both based on spurious arguments—should differ by almost an order of magnitude. The conclusion that exposure to ambient tobacco smoke produces ". . . about 5000 lung cancer deaths per year in U.S. nonsmokers aged > 35 years . . ." belongs more to speculation than reality. When we take into account the outcome of the randomized trials together with the paradoxical implications of the findings of Sandler *et al.* (1985a, 1985b), the best estimate of LCDs per year is approximately zero.

No methodologically sound investigation of putative carcinogenic effects of passive smoking has yet been carried out. In the light of the size and cost of the randomized trials of the effects of quitting smoking—and of the disappointing results—it must be doubted whether any methodologically sound study of the requisite sensitivity will be undertaken in connexion with passive smoking in the foreseeable future.

Repace and Lowrey may feel justified in—and can hardly be blamed for—following practices that, in spite of numerous warnings (Hill, 1949; Fisher, 1959; Brownlee, 1965; Yerushalmy, 1971; Feinstein, 1979) are still commonplace in epidemiology. In the words of a distinguished clinical epidemiologist, a "licensed" epidemiologist ". . . can obtain and manipulate the data in diverse ways that are sanctioned not by the delineated standards of science, but by the traditional practice of epidemiologists" (Feinstein, 1979). We must hope that, before further public alarm is generated, wiser and more scientific counsels will prevail.

References

Brownlee, K. A. (1965) A review of "Smoking and Health." *J. Am. Stat. Assoc.* **60**, 722–739.

Burch, P. R. J. (1981a) Passive smoking and lung cancer. *Brit. Med. J.* **282**, 1393.

Burch, P. R. J. (1981b) Smoking and mortality in England and Wales, 1950 to 1976. *J. Chron. Dis.* **34**, 87–103.

Burch, P. R. J. (1983) The Surgeon General's "Epidemiologic criteria for causality." A critique. *J. Chron. Dis.* **36**, 821–836.

Burch, P. R. J. (1984) The Surgeon General's "Epidemiologic criteria for causality." Reply to Lilienfeld. *J. Chron. Dis.* **37**, 148–156.

Burch, P. R. J. (1985) Lifetime passive smoking and cancer risk. *Lancet* **1**, 866.

Feinstein, A. R. (1979) Methodologic problems and standards in case-control research. *J. Chron. Dis.* **32**, 35–41.

Feinstein, A. R. (1985) Experimental requirements and scientific principles in case-control studies. *J. Chron. Dis.* **38**, 127–133.

Fisher, R. A. (1959) *Smoking. The Cancer Controversy*. Oliver & Boyd, Edinburgh, Scotland.

Hill, A. B. (1949) *Principles of Medical Statistics*. Lancet Ltd., London.

Hirayama, T. (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Brit. Med. J.* **282**, 183–185.

Jarvis, M. J. and Russell, M. A. H. (1984) Measurement and estimate of smoke dosage to non-smokers from environmental tobacco smoke. *Europ. J. Resp. Dis.* **65**, Suppl 133, 68–75.

Kabat, G. C. and Wynder, E. L. (1984) Lung cancer in nonsmokers. *Cancer*, **53**, 1214–1221.

Lilienfeld, A. M. (1983) The Surgeon General's "Epidemiologic criteria for causality": A criticism of Burch's critique. *J. Chron. Dis.* **36**, 837–845.

Matsukara, S., Taminato, T., Kitano, N., Seino, Y., Hamada, H., Uchihashi, M., Nakajima, H. and Hirata, Y. (1984) Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers. *New Engl. J. Med.* **311**, 828–832.

MRFIT Research Group (1982) Multiple risk factor intervention trial: Risk factor changes and mortality results. *J. Am. Med. Assoc.* **248**, 1465–1477.

Repace, J. L. and Lowrey, A. H. (1985) A quantitative estimate of

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nonsmokers' lung cancer risk from passive smoking, *Environ. Int.* 11, 3–22.

Rose, G., Hamilton, P. J. S., Colwell, L. and Shipley, M. J. (1982) A randomized controlled trial of anti-smoking advice: 10-year results, *J. Epidemiol. Commun. Health* 36, 102–108.

Sandler, D. P., Wilcox, A. J. and Everson, R. B. (1985a) Cumulative effects of lifetime passive smoking on cancer risk, *Lancet* 1, 312–315.

Sandler, D. P., Wilcox, A. J. and Everson, R. B. (1985b) Lifetime passive smoking and cancer risk, *Lancet* 1, 866–867.

U.S. Surgeon General (1982) The health consequences of smoking. Cancer. U.S. Department of Health and Human Services, Washington, DC.

Yerushalmy, J. (1971) Self-selection—A major problem in observational studies, in *Proc. 6th Berkeley Symp. on Mathematical Statistics and Probability*, vol. IV: *Biology and Health*, L. M. Le Cam, J. Neyman, and E. L. Scott, eds., pp. 329–342. University of California Press, Berkeley, CA.

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LETTER TO THE EDITORS

Introduction

Repace and Lowrey (1985) estimate exposure to environmental tobacco smoke (ETS) in Appendix A. In Appendix B they extrapolate an exponential dose response curve to the number of lung cancer deaths presumed to be caused by passive smoking in the community. In Appendix C they contrast lung cancer mortality in nonsmokers, comparing Seventh Day Adventists (SDAs) with a group of non-SDAs and then, assuming this difference to be caused solely by passive smoking, extrapolate the putative effect of passive smoking to the U.S. population to estimate the decrease in life expectancy presumed to be due to ETS.

In the following, I express the difficulties I have in accepting these estimates.

Appendix A

With regard to environmental tobacco smoke, I question whether "the daily exposure of individuals can be estimated" accuratedly using global statistics as described in appendix A. By definition, exposure occurs to a nonsmoker in the presence of an active smoker. Couples or groups containing at least one nonsmoker and one person smoking are the appropriate statistical units, not the individual! Such groups are dynamic, especially at the worksite. In general, smokers mix with smokers and nonsmokers with nonsmokers. Thus, office workers often control their own microenvironment. Likewise, at home, couples tend to be or to become alike in their smoking behavior. Consequently, it is quite difficult to estimate the typical nonsmoker's exposure to ETS accurately. It can be shown that the estimates given in this paper are overestimates, caused by the authors' disregard of the grouping of smokers and nonsmokers.

Consider, for example, the derivation of exposure in the home (exposure at the worksite is much more dynamic and variable from site to site). In Appendix A2 Repace and Lowrey consider adult couples in which the husband works and in which 42% of the wives are also employed. From their sources, only 37% of these couples have a nonsmoker exposed to ETS. Assuming that exposure requires contemporaneous occupation of the same space, it follows that these couples are together, at most, 34% of the waking day (the time given for the husband to be at home). Irrespective of which partner smokes the 32 cigarettes per day (cpd) assumed for a typical smoker, the nonsmoker is exposed at home to, *at most*, $32 \times 0.34 = 11$ cpd and this occurs in 37% of all two-person homes. Repace and Lowrey estimate the exposure to be 22 cpd in 62% of homes!

Now, consider Appendix A1 in which the exposure at the worksite is estimated. At no point in their argument do the authors consider the aggregation of smokers with smokers and nonsmokers with nonsmokers. Instead they assume a perfect mixing of smokers and nonsmokers in deriving their estimates. If, on the other hand, all smokers worked with smokers and nonsmokers with nonsmokers, then the global statistics they use would still describe the population but there would be zero exposure to ETS! Repace and Lowrey's estimates can only therefore be taken as an upper boundary to the upper limit of exposure to ETS.

Their method of estimation may also be criticised on theoretical grounds. Here and elsewhere in the paper the authors multiply averages and assume that the resultant product is the average of the convolution of the two original statistical distributions. This is true only if the two variates are independent. If not, then

$$E(xy) = E(x) \cdot E(y) + \rho\sigma_x\sigma_y,$$

where ρ is the correlation coefficient of x and y, σ is the standard deviation, and E is the expectation or average. It is likely that the variate, air exchange rate, is positively correlated with both density of occupation and with respiration rate, and that duration of exposure is negatively correlated with density of occupation and with respiration rate. The combined effect of these associations are unknown.

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Appendix B

In Appendix B, the model is given as

$$P(D) = 1 - \exp(bD),$$

where D is the exposure, b is a constant, and $P(D)$ is the risk of a lung cancer death. The use of this model may be criticised on the following grounds:

- the relationship of passive smoking with lung cancer has *not* been shown to be a cause and effect relationship so that such modelling is, at best, premature;
- "the assumption of a no-threshold effect for carcinogens is also unproved" (Abelson, 1984);
- "the ambient measurements may have little or no bearing on the amounts that actually reach the target tissue" (Doll, 1985).

Thus, it is unlikely that such a simple model will adequately describe a complex process of carcinogenesis. A more general approach recognizes that tumor response is a function of delivered dose, D^* and that D^* is a *nonlinear* function of D, the exposure. Thus, the one-hit model

$$P = 1 - \exp(-[a + bD])$$

is a special case of this relationship (Hoel *et al.*, 1983) where D has been substituted for D^*. Hoel *et al.* (1983) give scenarios in which the 'standard approach,' extrapolated below the range of observed values underestimates the dose required for a given tumor incidence by factors of 50 to 100. The "hockey stick" relationship for carcinogens whose metabolites form DNA adducts can easily be taken for a straight line relationship if the minimum observed exposure is above the curve on the "hockey stick" (Hoel *et al.*, 1983). In a comparable situation to environmental tobacco smoke, the delivered dose/administered dose of formaldehyde in ambient air was shown to be significantly nonlinear (Casanova-Schmitz *et al.*, 1984). Starr and Buck (1984) show that four common dose-response models, the probit, logit, Weibull and multistage, all fitted the observed data on cancer risk from formaldehyde inhalation and could not therefore be discriminated among on the grounds of goodness of fit. Assuming that these models can be compared in fitting both administered and delivered dose curves, Starr and Buck (1984) show that, in all models the use of delivered dose gave lower estimates and lower upper confidence limits of cancer risk for a given low administered dose. More important, the range of the upper confidence limits increased among models as the administered dose fell.

In the above two studies the examples are based on animal exposures with zero tumors at zero dose. The one-hit model used by Repace and Lowery likewise has a zero intercept term. This is equivalent to assuming that the mortality rate of lung cancer is zero in the absence of ETS. Thus, yet again, Repace and Lowrey assume ETS to be the sole cause of lung cancer in the nonsmoker!

Appendix C

Here, Repace and Lowrey (1985) use unpublished data on lung cancer deaths (LCDs) in two groups of nonsmokers, followed roughly for the same period. If we accept that biases in ascertainment, classification and recording of LCDs are comparable in these two groups of SDAs and non-SDAs, then what? As before, Repace and Lowrey (1985) ascribe this difference solely to differences in exposure to environmental tobacco smoke (ETS). We are not, however, given the death rates from other causes of death in these two groups. If the death rates for motor vehicle accidents differ in the two groups, would Repace and Lowrey ascribe this difference likewise to differences in ETS? Again if mortality from cancer of the reproductive system is higher in SDA women than in non-SDA nonsmokers, would Repace and Lowrey assume that passive smoking had a protective effect?

In an editorial comment on a prospective study over a 20-yr period, the conclusion is questioned that eating fish is beneficial to health, although a lower mortality from heart disease is demonstrated. The editor points out that fish consumption may be associated with higher rates from other causes of death (Glomset, 1985). A similar problem exists with this method of estimation.

Conclusion

In some situations, a case can be made for reversing the usual definitions of the null and alternative hypotheses (Anderson and Hauck, 1983). This, however, is *not one of them*. The null hypothesis that passive smoking and lung cancer mortality are causally unrelated still stands. Until it is rejected, I consider it irresponsible to apply risk management techniques, even if they had been applied correctly.

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References

Abelson, P. H. (1984) Environmental risk management (editorial). *Science* 226, 4678, 1023.

Anderson, S. and Hauck, W. W. (1983) A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Comm. Stat. Theor. Meth.* 12, 2663–2692.

Casanova-Schmitz, M., Starr, T. B., and Heck, H. d'A (1984) Dif-

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ferentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow by inhaled [^{14}C] and [^{3}H] formaldehyde. *Toxicol. Appl. Pharmacol.* 76, 26–44.

Doll, R. (1985) Occupational cancer: A hazard for epidemiologists. *Int. J. Epidemiol.* 14, 22–31.

Glomset, J. A. (1985) Fish, fatty acids, and human health. *New Eng. J. Med.* 312, 1253–1254.

Hoel, D. G., Kaplan, N. L. and Anderson, M. W. (1983) Implication of nonlinear kinetics on risk estimation in carcinogens. *Science* 219, 1032–1047.

Repace, J. L. and Lowrey, A. H. (1985) A quantitative estimate of nonsmokers' lung cancer risk from passive smoking. *Environ. Int.* 11, 3–22.

Starr, T. B. and Buck, R. D. (1984) The importance of delivered dose in estimating low-dose cancer risk from inhalation exposure to formaldehyde. *Fund. Appl. Toxicol.* 4, 740–753.

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Lung cancer and passive smoking: predicted effects from a mathematical model for cigarette smoking and lung cancer

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Summary Epidemiological studies of active smokers have shown that the duration of smoking has a much greater effect on lung cancer risk than the amount smoked. This observation suggests that passive smoking might be much more harmful than would be predicted from measures of the level of exposure alone, as it is often of very long duration frequently beginning in early childhood. In this paper we have investigated this using a multistage model with five stages. The model is shown to provide an excellent fit to data on the incidence of lung cancer among smokers, ex-smokers and non-smokers in a cohort of male British doctors. Contrary to our expectation the model predicted only a slight increase in relative risk with increasing duration of passive exposure. Allowing for exposures early in life does not therefore explain the discrepancy between the relative risk of about 1.5 calculated from epidemiological studies of lung cancer and the low levels of exposure indicated by cotinine measurements in those passively exposed.

It has been suggested, using data from epidemiological studies of lung cancer and passive smoking (i.e. exposure to other people's tobacco smoke), that the relative risk of lung cancer among non-smokers living with smokers, compared to non-smokers living with non-smokers is about 1.5 (see, for example, Wald *et al.*, 1986). This estimate of relative risk is considerably higher than one would predict on the basis of studies of cotinine levels in non-smokers living with smokers (Committee on Passive Smoking, 1986). It is clear that epidemiological studies of passive smoking are particularly difficult to carry out because of the large errors inherent in obtaining adequate histories of such past exposure and because the studies need to avoid even slight biases as the relative risks involved are small.

Epidemiological studies of active smokers have however shown that the duration of smoking has a much greater effect on lung cancer risk than the amount smoked. For example heavy smokers (30 cigarettes per day) of 15 years duration have been shown to have only about one tenth the excess lung cancer risk of moderate smokers (15 cigarettes per day) who have smoked for 30 years, although the total number of cigarettes smoked is the same (Peto & Doll, 1984). This observation suggests that exposure to tobacco smoke at the low levels incurred during passive smoking might be much more harmful than would be predicted from measures of the level of the exposure alone, as passive exposure is often of very long duration frequently beginning in early childhood.

In this paper we have investigated the possible effects of such long duration exposure to passive smoking starting in childhood by modelling the effect of cigarette smoke on lung cancer incidence using a multistage model, and compared the estimates so obtained to those observed in epidemiological studies.

A multistage model for lung cancer

The model

The idea that a cancer is generated only after a cell has undergone a series of distinct, ordered, transformations or 'stages' was introduced to explain the observation that the mortality rates for many sites of cancer that are epithelial in origin increase as the fourth, fifth, or sixth power of age. Multistage models have also been highly successful in describing many features of experimental carcinogenesis, for a review see Peto (1977) or Day (1983). The model as proposed originally by Armitage & Doll (1961) is the best known formulation and a brief description of it is given in the **Appendix**. In this formulation, if there are k stages involved for the cancer in question (normal cell = stage '0', stage 1, ..., stage k = cancer cell), we denote the probability that a cell which is at stage $i-1$ transforms into stage i in unit time as a a_i, $i=1,\ldots,k$. According to this model, if these a_i remain constant throughout life, and if the time for a fully transformed malignant cell to grow into a clinically detectable tumour is ignored, then the incidence rate at age t will be proportional to t^{k-1}. It follows that if the logarithm of the age-specific incidence rates are plotted against the logarithm of age, then the plotted points will fall on a straight line with slope $k-1$.

Data on the incidence of lung cancer in non-smoking US males have been published by Kahn (1966) and Hammond (1966), and together include 127 cases of lung cancer. The data have been combined by Doll (1971) and are reproduced in Figure 1. It can be seen that they lie very close to a straight line with slope four, indicating that five stages are appropriate in the model for lung cancer. Among regular cigarette smokers the incidence rises more rapidly with age, and the slope of the line is about seven, but when the rates are plotted against duration of smoking, rather than age, the incidence again rises approximately as the fourth power, see Figure 1 (Doll, 1971).

In order to understand which stages in the multistage model are affected by smoking, it is necessary to consider the following two critical epidemiological observations. Firstly the fact that age at starting to smoke and duration of smoking are critical determinants of lung cancer risk, and secondly the fact that after stopping smoking the incidence rate remains approximately at the level when smoking stopped (Doll & Peto, 1976). In terms of the multistage model, these can be shown to imply that cigarette smoke has a strong effect on an early stage, probably the first, and also that it affects a late stage, but not the last (Doll, 1978; Day & Brown, 1980). When attention is restricted to smokers of cigarettes only, who also have a record of unchanging smoking habits, the relation between lung cancer incidence and number of cigarettes smoked per day is greater than linear, see Figure 2, and this provides additional evidence that more than one stage in the process is affected (Doll & Peto, 1978).

In the present paper we first show that a multistage model

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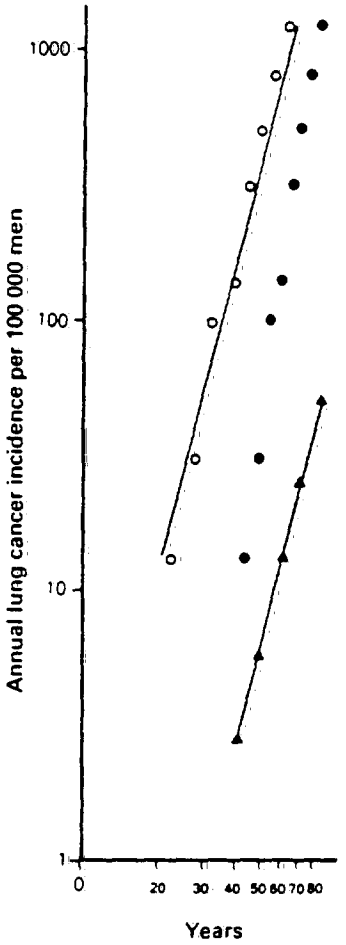

Figure 1 Incidence of bronchial carcinoma in non-smokers by age (▲) and in regular cigarette smokers by age (●) and duration of smoking (○). Solid lines have slope 4. Data for non-smokers from Doll (1971, Table VI). Data for smokers from Doll & Peto (1978) Table II, directly standardized for amount smoked.

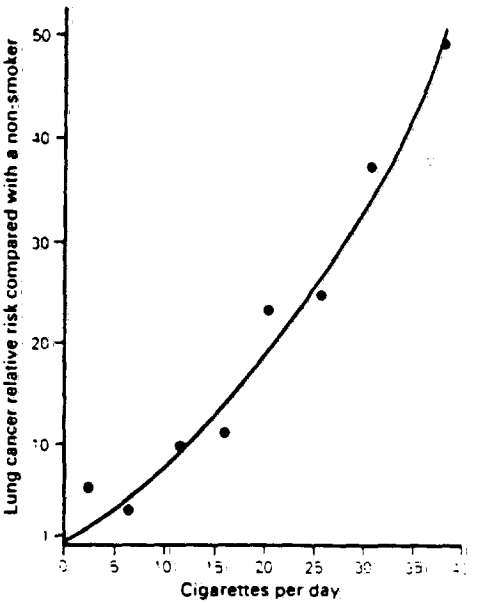

Figure 2 Comparison of dose-response observed in British doctors' study with that obtained from the proposed multi-stage model. ● – Relative risks indirectly standardized for age from Doll & Peto (1978), Table IV. (Printed values have been divided by 0·081 so that 0 cigarettes per day takes value 1.) Solid line – Relative risks predicted from the model. Values plotted are weighted sums of age-specific relative risks with weights equal to those used by Doll & Peto (1978), Table IV, for indirect standardization.

with five stages in which cigarette smoke affects the first and the fourth stage provides a highly satisfactory description of the patterns of lung cancer observed among active cigarette smokers. The patterns of lung cancer risk predicted by the model when the quantity of cigarettes smoked per day is very low, such as might effectively be smoked under conditions of passive exposure, are then explored.

Active smokers

Data on the numbers of lung cancers diagnosed and the distribution of man-years from a 20-year prospective study of male British doctors have been published by Doll & Peto (1978) for people who either reported that they were lifelong non-smokers, or who reported that they had smoked cigarettes regularly since early adult life, without either giving up or changing their consumption by more than five cigarettes per day, and who also reported no current or previous use of cigars or pipe. The data are available in the form of numbers of diagnosed lung cancers and man-years at risk in Tables II and III of Doll & Peto (1978) by current age in five-year groups, and numbers of cigarettes smoked per day (Never smoked, 1–4, 5–9, 10–14, etc.).

The lung cancer risk at age t, as predicted by our multistage model, for an individual who started smoking at age s and from then on smoked c cigarettes per day, relative to a lifelong non-smoker, is given in the **Appendix**. It depends on two parameters, b_1 and b_4, which are respectively the proportional amounts by which the rate of transformations to the first and the fourth stages of the carcinogenic process are increased by each cigarette smoked per day; specifically a_1 becomes $a_1(1+cb_1)$ and a_4 becomes $a_4(1+cb_4)$ during the time in which c cigarettes per day are smoked. The values of the parameters b_1 and b_4 were estimated by the method of maximum likelihood, conditional on the total number of incident lung cancers in each age group, and using data from the British doctors' study for individuals who were aged from 40 to 79 years, and who smoked up to 40 cigarettes per day. We have ignored data on doctors who reported smoking more than 40 cigarettes/day, as did Doll and Peto in their analysis; a full discussion of the reasons for omitting them is given in Doll & Peto (1978). In the data all the doctors had started smoking when they were between 16 and 25 years old. In estimating b_1 and b_4 it was assumed for simplicity that all the smokers had started smoking at 20 years of age. This method of fitting enables the effect of cigarette smoking to be estimated in terms of relative risks. To make predictions in terms of absolute incidence rates we have assumed in what follows that the incidence rate in non-smokers at age 60 is equal to that observed in the data on non-smokers in Figure 1.

The estimated values for b_1 and b_4 are 0.29 and 0.37 with estimated standard errors of 0.32 and 0.35. The fit of the model to the British doctors' data is excellent. Pearson's goodness-of-fit statistic is 52.4 and the residual deviance is 51.1; both of these statistics have 54 degrees of freedom and thus provide no evidence of a poor fit to the data. A plot of standardized residuals against normal order statistics indicated that the model fitted the data well, and plots of residuals against both current age and number of cigarettes smoked per day gave no evidence of systematic departures from the model.

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The ability of the model to reproduce the main features of cigarette smoking, as observed in the British doctors' study, is illustrated in Figures 2 to 4. In Figure 2 it can be seen that the dose response relationship from the multistage model reproduces very closely the approximately quadratic relationship observed in the data. Figure 3 shows the annual incidence of lung cancer in smokers and non-smokers as predicted by the model. The predictions have been made assuming that all smokers started smoking on reaching age 20, and smoked 20 cigarettes per day. These values are similar to the average values of 19.2 years and 18 cigarettes per day observed in the British doctors' data. By comparing Figures 1 and 3 it can be seen that, once again, the proposed model reproduces very closely the patterns of increase in lung cancer incidence seen in the original data.

Figure 4a shows data on the risk of lung cancer among British doctors who stopped smoking, by time since stopping, relative to their risk at the time they stopped. For comparison, risks are shown on the same scale for continuing cigarette smokers and lifelong non-smokers. The beneficial effect of stopping smoking is evident within five years, and there is a possibility that the incidence rate may actually decrease during the first 10 years after stopping smoking. However, the data are too few to be certain that this is so, and it is clear that the risk keeps well above that for lifelong non-smokers (Doll, 1978). The equation predicting the effect of giving up smoking according to the multistage model is given in the **Appendix**, and it is illustrated in Figure 4b, where it is assumed that the smokers consumed 20 cigarettes per day from age 20 to age 50 and then stopped. As was seen in the doctors' study, the beneficial effect of stopping is seen after only a few years, and the risk among those who stopped is clearly intermediate between those seen in continuing smokers and in lifelong non-smokers. From the model predictions there is no suggestion that the relative risk falls below one in the first

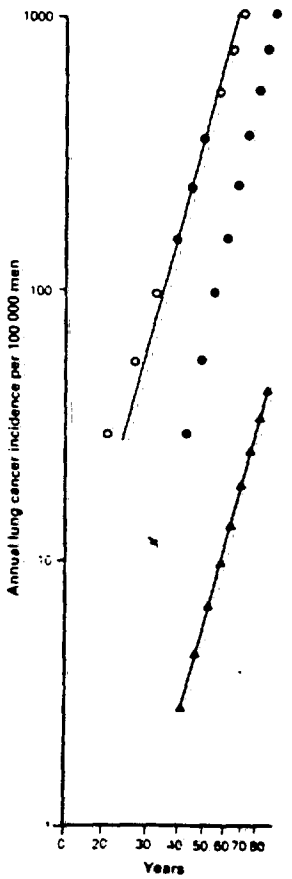

Figure 3 Incidence of bronchial carcinoma as predicted by the model in non-smokers by age (▲) and in smokers of 20 cigarettes per day from age 20 by age (●) and duration of smoking (○). Solid lines have slope 4.

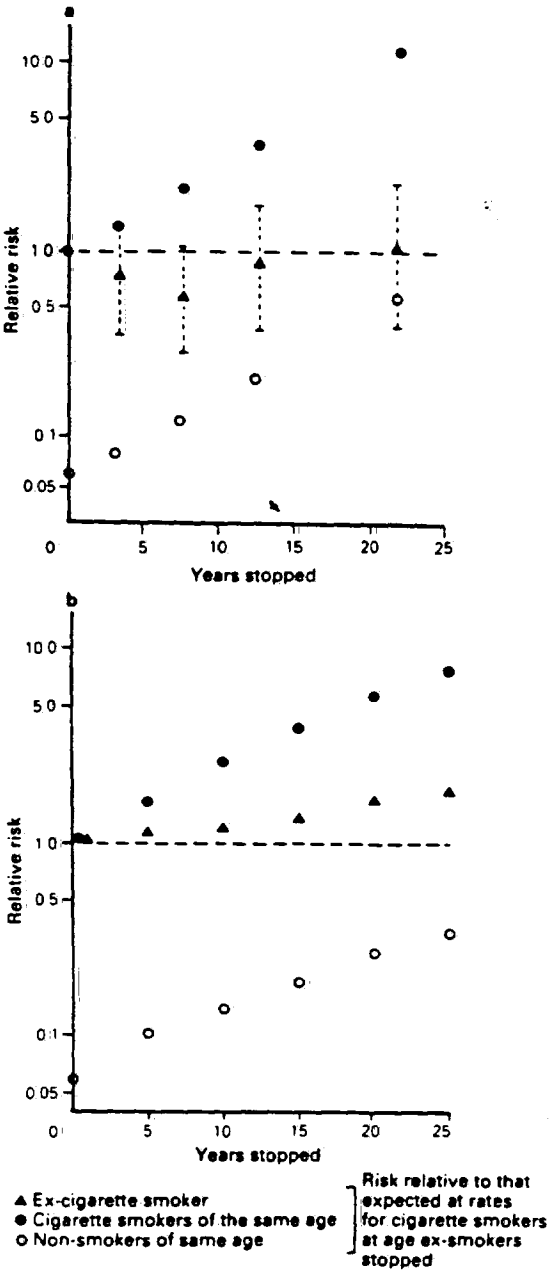

Figure 4 Comparison of the effect of stopping smoking observed in British doctors' study with that obtained from the proposed multistage model. Risk is measured relative to the risk in a regular cigarette smoker at the ages at which smoking was stopped (a) Data from British doctors' study, and US non-smokers standardized for amount smoked at time of stopping. (Data from Doll, 1978, chart 6, reproduced with permission.) (b) Predictions from the model, assuming smokers consumed 20 cigarettes per day from age 20 to age 50, and then stopped.

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few years after stopping, and using the equation for the relative risk in an ex-smoker shown in the **Appendix** it can be shown that under the proposed model the incidence of lung cancer will never decrease below that already reached at the time of stopping smoking regardless of amount smoked or ages at starting and stopping. There is evidence from pathological studies of tracheo-bronchial trees that the number of atypical nuclei in the bronchial epithelium diminishes on cessation of smoking (Auerbach *et al.*, 1962), and this observation lends some support to the idea that the risk of lung cancer might actually decrease in the first few years after giving up smoking. However, the slight discrepancy between the observations on British doctors and the predictions from the model could also be accounted for by random variation, or by the fact that individuals who succeed in giving up smoking were less likely to inhale than continuing smokers (Doll & Hill, 1964).

Overall the ability of this multistage model to reproduce the main features of cigarette smoking, as observed in the British doctors' study seems remarkable.

Passive smoking

The predictions of the model when the number of cigarettes smoked per day is low, including the range of exposures indicated by the risks observed in epidemiological studies of passive smoking, are shown in Table I. The predictions have been made for an individual aged 65 assuming first that the individual was exposed continuously from birth, secondly that the individual was unexposed until age 20 but exposed continuously since then, as might happen for a non-smoking individual who married a smoker or started work in a smoky environment at age 20, and thirdly that the individual was exposed only between birth and age 20, as might occur in individuals whose parents smoked, but who were not otherwise exposed. A number of points emerge. First, on a relative scale at least, the risks are substantial. The predicted effect of smoking the equivalent of only one cigarette per day from birth to age 65 is to increase lung cancer risk by more than 75%, while if exposure starts at age 20 the risk is increased by 46% and if exposure is limited to childhood the risk is increased by 23%. Secondly, for exposures up to the equivalent of three cigarettes per day, exposure in childhood only is predicted to incur about half the increase in risk of exposure at the same level in adult life only. Thirdly, and most strikingly, although the risk is greater if exposure occurs both in childhood and in adult life than if it occurs in only one of the two periods, the drastic increase in risk with increasing duration of exposure, seen in active smokers, is absent. For example, exposure at the rate of one cigarette per day from birth to age 65 incurs only a 21% greater relative risk than exposure at the rate of one cigarette per day from age 20 to age 65 (1.77 compared with 1.46). Direct analogy with the effect of duration of smoking as seen in active smokers of around 20 cigarettes per day would have predicted nearly a four-fold increase.

The importance of duration of exposure in determining the increase in relative risk diminishes with diminishing level of exposure. This is illustrated in Table II where the lung cancer relative risks predicted by the model are shown for a wide range of levels of exposure. For smokers of 20 cigarettes per day, relative risks by age 60 are more than 50% greater than they were at age 40, but at low levels, such as half a cigarette per day, the proportionate increase in relative risk is less than 3% over the same period.

The above calculations have all been made assuming that the British doctors were not themselves exposed to passive smoke. As regards exposure in childhood this assumption is

Table I Effect of passive smoking on lung cancer risk at age 65, as predicted by the model

Effective passive smoking (cigarettes per day equivalent)	*Risk relative to a non-exposed non-smoker*		
	Exposure from age 0 to age 65	*Exposure from age 20 to age 65 only*	*Exposure from age 0 to age 20 only*
0.00	1.00	1.00	1.00
0.10	1.07	1.04	1.02
0.20	1.14	1.09	1.05
0.25	1.17	1.11	1.06
0.50	1.36	1.22	1.11
1.00	1.77	1.46	1.23
1.50	2.23	1.71	1.34
2.00	2.75	1.97	1.46
3.00	3.95	2.52	1.69
4.00	5.36	3.13	1.93
5.00	6.98	3.78	2.16

Table II Lung cancer risk predicted from the model for smoking a constant number of cigarettes per day starting at age 20. Figures shown are risks relative to that for a non-exposed non-smoker by current age and number of cigarettes per day

Current age	*Cigarettes per day*						
	0.1	*0.5*	*1.0*	*5.0*	*10.0*	*20.0*	*30.0*
40	1.036	1.184	1.37	2.99	5.31	10.96	17.94
50	1.040	1.202	1.41	3.33	6.36	14.50	25.42
60	1.042	1.216	1.44	3.64	7.33	17.90	32.71
70	1.044	1.228	1.47	3.91	8.21	21.01	39.39
80	1.046	1.238	1.49	4.14	8.99	23.76	45.32
Above relative risks divided by relative risk at age 40:							
40	1.000	1.000	1.00	1.00	1.00	1.00	1.00
50	1.003	1.016	1.03	1.12	1.20	1.32	1.42
60	1.006	1.027	1.05	1.22	1.38	1.63	1.82
70	1.008	1.037	1.07	1.31	1.55	1.92	2.19
80	1.009	1.046	1.09	1.39	1.69	2.17	2.52

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probably reasonable, as all individuals would have dates of birth before about 1926. In the 1920s cigarette consumption among women (including the mothers of the British doctors) was very low, while that among men was less than in subsequent years (Lee, 1976). In contrast, passive exposure in adult life may well have been substantial in the doctors' cohort by present day standards, as the vast majority of men, doctors included (Doll & Peto, 1976), smoked cigarettes in 1951 when the cohort was identified, and when there was little public awareness of the risks of either active or passive smoking. In order to illustrate the possible effect of passive smoking among the British doctors on the predictions shown in Table I, estimates of the parameters in the multistage model were recalculated assuming, as an example, that all the doctors, both smokers and non-smokers, were exposed to passive cigarette smoking at a rate equivalent to one cigarette per day throughout their adult life. The revised model predictions from this example are shown in Table III. The general effect of making the allowance for passive smoking is a small increase in the predicted relative risks which is of the order of 10 to 20% for passive smoking exposures of half to one cigarette per day equivalent. For exposures of five cigarettes per day, larger increases in relative risk are implied, and for an individual who has been exposed at a rate of five cigarettes per day from age 20 the predicted risk at age 65 relative to a lifelong non-smoker is increased by nearly 40% from 3.78 to 5.24. However the general conclusions based on the predictions in Table I remain unchanged. In practice non-smokers are, of course, likely to have much less passive smoking exposure than smokers; when this is taken into account the changes shown in Table III are, of course, reduced and the true effects are thus likely to be bounded by the results in Table I and Table III.

Discussion

Multistage models for the development of cancer are possibly no more than a crude mathematical description of a complex biological process. Nevertheless the proposed multistage model has been shown to provide an accurate coherent summary of the patterns of lung cancer risk among active smokers, ex-smokers, and non-smokers. It is likely therefore also to provide good estimates of the pattern of lung cancer risk following exposure equivalent to smoking between 0.1 and five cigarettes per day. It should also provide a reasonable guide to the consequences of environmental exposure to other people's smoke (passive smoking). It should in particular provide guidance on topics on which accurate human data is likely to remain sparse, such as the likely effects of variation in the age at which passive exposure began and of variation in the duration of such exposure, although of course in the absence of validatory data it cannot be concluded with certainty that the model predictions in this low dose range are correct.

Among active smokers, age at starting to smoke and duration of the smoking habit strongly determine the risk of lung cancer, and these features are accommodated in our model by the assumption that exposure to cigarette smoke affects the first stage. We therefore anticipated that the model would predict a substantial increase in relative risk for exposures starting in early childhood. However, our expectations were not supported by the model predictions, which indicate an increase in the relative risk of no more than about 20% for exposure starting at birth compared to exposure starting at age 20, for exposures equivalent to the range one tenth to one cigarette per day. If the 'adult exposure' had been assumed to start at an earlier age than 20, reflecting the fact that in recent surveys in Britain the median recalled age at starting to smoke is 16–17 (Wald *et al.*, 1988), the increase in relative risk for lifelong exposure, as compared with exposure in adult life only, would have been even smaller.

The relative risks associated with exposures in the range one tenth to one cigarette per day are less than two, and are thus smaller than the underlying background risk of lung cancer due to causes other than cigarettes. Exposure to at least some of these is likely to commence at birth or in early childhood. On this basis it is more helpful to think of the early commencement of passive smoking at rates equivalent to one cigarette per day or less as an increase in the dose of an existing carcinogenic exposure rather than an increase in the duration of passive smoking exposure.

In terms of the mathematical formulation of the model given in the **Appendix**, it is clear from the expression for $P(s,t)$, the incidence rate at age t in the smoker of c cigarettes per day since age s, that as c increases the term involving $c^2 b_1 b_4$, which involves duration to the fourth power, will begin to dominate. For small values of c (i.e. less than b_1^{-1} and b_4^{-1}) it can easily be shown that the term involving cb_4, which increases only very slowly with duration, will play the major role in determining the incidence rate for values of b_1, b_4, s and t that are of concern here. In non-mathematical terms this amounts to the fact that, for active smokers of a substantial number of cigarettes, the incidence rate of lung cancer is determined by the effect of smoking on both the first and the fourth stages. In contrast, at levels equal to the numbers of cigarettes effectively smoked by passive smokers, the effect of those cigarettes is primarily on the fourth stage, and its effect on the first stage is relatively minor.

Wald *et al.* (1986) have reviewed the 13 epidemiological studies of lung cancer and passive smoking which have been carried out in six different countries. When the results are combined, these studies suggest that the relative risk of lung

Table III Effect of passive smoking on lung cancer risk at age 65, as predicted by the model, allowing for passive smoking at a rate equivalent to smoking one cigarette per day from age 20 in the British doctors

Effective passive smoking (cigarettes per day equivalent)	*Risk relative to a non-exposed non-smoker*		
	Exposure from age 0 to age 65	*Exposure from age 20 to age 65 only*	*Exposure from age 0 to age 20 only*
0.00	1.00	1.00	1.00
0.10	1.09	1.06	1.03
0.20	1.19	1.13	1.05
0.25	1.23	1.16	1.06
0.50	1.49	1.33	1.13
1.00	2.07	1.68	1.25
1.50	2.75	2.05	1.38
2.00	3.51	2.44	1.51
3.00	5.31	3.29	1.76
4.00	7.48	4.22	2.03
5.00	10.01	5.24	2.29

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cancer among non-smokers living with smokers compared to non-smokers living with non-smokers is about 1.35. Wald *et al.* estimated that adjustment for the likely extent of misclassification of some current smokers and some ex-smokers as non-smokers (never-smokers) reduces this estimate to 1.30, but estimated that allowance for the fact that people living with non-smokers may still be exposed to other people's smoke increases the estimate to 1.53. (This latter adjustment is similar in magnitude to the effect of allowing for exposure to environmental tobacco smoke among the British doctors in estimating the parameters of our multistage model, see Table III.)

Although the US National Academy of Science's Committee on Passive Smoking (1986) accepted the estimates of Wald *et al.*, other authors have disputed them and claimed that the increased lung cancer risk seen among non-smokers exposed to passive smoking is largely the effect of bias due to the misclassification problems we mentioned above. For example, Lee (1987) suggested, on the basis of recent surveys carried out in the UK for the Tobacco Advisory Council, that the proportion of true ex-smokers amongst persons claiming to be lifelong non-smokers was double the estimate used by Wald *et al.* Lee also suggested that the average number of cigarettes per day smoked by current smokers claiming to be non-smokers was considerably more than estimated by Wald *et al.* and was at least half that of people admitting to being smokers. These assumptions lead to a much lower estimate for the lung cancer risk from passive smoking, and Lee concluded that almost no lung cancer is caused by passive smoking. In our opinion, Lee's estimate of the average number of cigarettes smoked per day (an important determinant in the risk estimation) among current smokers claiming to be non-smokers seems excessive, but it is hard to judge on the basis of published data how either the estimates of Wald *et al.* or Lee relate to the individual studies that led to the combined estimate of 1.35. Further work is required on the extent of misclassification in the actual populations in which the epidemiological studies were done.

The biological marker that has proved most useful in assessing average daily exposure to tobacco smoke among those exposed to passive smoking is cotinine (Committee on Passive Smoking, 1986). Recent studies in the UK measuring cotinine levels in active and passive smokers in plasma, urine and saliva indicate that levels in passive smokers are in the range 0.6 to 0.8% of those in active smokers (Jarvis *et al.*, 1984). However the half-life of cotinine in non-smokers may be roughly 50% longer than in active smokers (Sepkovic *et al.*, 1986). Active smokers in the UK currently smoke between 15 and 20 cigarettes per day (Wald *et al.*, 1988) and so the cotinine measurements indicate an exposure of between 0.06 and 0.11 cigarettes per day. According to the proposed multistage model, a relative risk of 1.5, as estimated by Wald *et al.* (1986) from the epidemiological studies of exposure to passive smoking, results from the effective exposure to about half to one cigarette per day. Thus the cotinine measurements indicate a level of exposure that is between one seventeenth and one fifth the amount indicated by our model. This estimate is based on cigarettes available during the 1950s and 1960s and used by the men in the British doctors' study: to the extent that currently available cigarettes are associated with lower lung cancer risks these factors would be somewhat reduced. A further difficulty is that the relationship between the amount of nicotine absorbed, and the amount of tar deposited on the bronchi is not necessarily the same in passive as in active smoking, and this could influence the postulated risk in either direction. We conclude, however, that the relative risks of lung cancer due to passive smoking as estimated by Wald *et al.* (1986) seem to be at variance with the numbers of cigarettes per day equivalent estimated from cotinine measurements. This discrepancy remains even when allowance is made, within the framework of our model, for the fact that passive smoking may commence in early childhood, and when the parameters of the model are estimated allowing the British doctors' themselves to have been exposed to passive smoking.

References

ARMITAGE, P. & DOLL, R. (1961). Stochastic models for carcinogenesis. In: *Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability*, Neyman, J. (ed) 4, p. 19. University of California Press: Berkeley and Los Angeles.

AUERBACH, O., STOUT, A.P., HAMMOND, E.C. & GARFINKEL, L. (1962). Bronchial epithelium in former smokers. *N. Engl. J. Med.*, 267, 119.

COMMITTEE ON PASSIVE SMOKING (1986). *Environmental Tobacco Smoke. Measuring Exposures and Assessing Health Effects*. National Academy Press: Washington D.C.

DAY, N.E. (1983). Time as a determinant of risk in cancer epidemiology: The role of multi-stage models. *Cancer Surveys*, 2, 577.

DAY, N.E. & BROWN, C.C. (1980). Multistage models and primary prevention of cancer. *J. Natl Cancer Inst.*, 64, 977.

DOLL, R. (1971). The age distribution of cancer: Implications for models of carcinogenesis. *J. R. Statist. Soc., A.*, 134, 133.

DOLL, R. (1978). An epidemiological perspective of the biology of cancer. *Cancer Res.*, 38, 3573.

DOLL, R. & HILL, A.B. (1964). Mortality in relation to smoking: Ten years' observations of British doctors. *Br. Med. J.*, 1, 1399.

DOLL, R. & PETO, R. (1976). Mortality in relation to smoking: 20 years' observations on male British doctors. *Br. Med. J.*, 2, 1525.

DOLL, R. & PETO, R. (1978). Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J. Epidemiol. Comm. Hlth*, 32, 303.

HAMMOND, E.C. (1966). Smoking in relation to the death rates of one million men and women. In *Epidemiological Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph 19, p. 127. U.S. Government Printing Office: Washington D.C.

JARVIS, M., TUNSTALL-PEDOE, H., FEYERABEND, C., VESEY, C. & SALOOJEE, Y. (1984). Biochemical markers of smoke absorption and self reported exposure to passive smoking. *J. Epidemiol. Comm. Hlth*, 38, 335.

KAHN, H.A. (1966). The Dorn study of smoking and mortality among U.S. veterans: Report on eight and one-half years of observation: In *Epidemiological Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph 19, p. 1. U.S. Government Printing Office: Washington D.C.

LEE, P.N. (ed) (1976). *Statistics of Smoking in the United Kingdom*. Research Paper 1, 7th edition. Tobacco Research Council: London.

LEE, P.N. (1987). Passive smoking and lung cancer association: A result of bias? *Human Toxicol.*, 6, 517–524.

PETO, R. (1977). Epidemiology, multi-stage models and short term mutagenicity tests. In *Origins of Human Cancer*, Hiatt, H.H. *et al.* (eds) 4, p. 1403. Cold Spring Harbor Laboratory.

PETO, R. & DOLL, R. (1984). The control of lung cancer. In: *Lung Cancer: Cases and Prevention*, Mizell, M. & Correa, P. (eds). Verlag Chemie International: Deerfield Beach, Florida.

SEPKOVIC, D.W., HALEY, N.J. & HOFFMANN, D. (1986). Elimination from the body of tobacco products by smokers and passive smokers. *J. Am. Med. Assoc.*, 256, 863.

WALD, N.J., NANCHAHAL, K., THOMPSON, S.G. & CUCKLE, H.S. (1986). Does breathing other people's tobacco smoke cause lung cancer? *Br. Med. J.*, 293, 1217.

WALD, N., DOLL, R., DARBY, S., KIRYLUK, S., PETO, R. & PIKE, M. (eds) (1988). *U.K. Smoking Statistics*. Oxford University Press.

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Appendix

It is assumed that there are five ordered stages in the carcinogenic process, that the rate of transition of a cell from stage to stage is constant in time apart from specified increases in the exposure intensity, that tumour growth time is negligible and that tumours are rare.

Let $P_4(t)$ be the probability that a specific cell has undergone four changes at time t. When exposure is to background exposure intensities only, let $P_4(t)$ be denoted by $P_4^0(t)$, and let the transition rates from stage to stage be a_i, $i=1,\ldots 5$. It follows that

$$P_4^0(t) = k_1 \int_0^t a_4 \int_0^{x_4} a_3 \int_0^{x_3} a_2 \int_0^{x_2} a_1 \, dx_1 dx_2 dx_3 dx_4$$

$$= k_1 a_4 a_3 a_2 a_1 t^4/4!$$

where k_1 is a constant. If $I^0(t)$ is the associated incidence rate of lung cancer for a background only exposed individual at age t, then

$$I^0(t) = k_2 a_5 P_4^0(t)$$

$$= k_3 a_5 a_4 a_3 a_2 a_1 t^4/4!,$$

where k_2 and k_3 are constants that include an allowance for the number of cells in the individual at risk of developing lung cancer.

For an individual who begins to smoke cigarettes at age s at the rate of c cigarettes per day and continues to smoke until age t, let the transition rate from stage zero to stage one be altered from a_1 to $a_1(1+cb_1)$ after age s, and similarly let that for stage three to stage four be altered from a_4 to $a_4(1+cb_4)$. In such a smoker, let the probability that in any individual cell the first $(i-1)$ transitions occur before age s, and the remaining $(5-i)$ after that age be denoted by $P_4^{(i)}(s,t)$ for $i=1,\ldots 4$. Then

$$P_4^{(i)}(s,t) = k_1 \int_0^t a_4^* \int_0^{x_4} a_3^* \ldots \int_0^{x_{i+1}} a_i^* dx_i \ldots dx_4$$

$$\times \int_0^s a_{i-1} \int_0^{x_{i-1}} a_{i-2} \ldots \int_0^{x_2} a_1 \, dx_1 \ldots dx_{i-1},$$

where $a_4^* = a_4(1+cb_4)$, $a_3^* = a_3$, $a_2^* = a_2$, and $a_1^* = a_1(1+cb_1)$, and the probability, $P_4^s(s,t)$, that the smoker has a specific cell that has undergone 4 changes at time t is given by

$$P_4^s(s,t) = \sum_{i=1}^{5} P_4^{(i)}(t).$$

It follows straightforwardly from substitution that the lung cancer incidence rate at age t in the smoker of c cigarettes per day since age s, $I^s(s,t)$, is given by

$$I^s(s,t) = k_3 a_5 a_4 a_3 a_2 a_1 t^4/4! \times [1 + cb_1(t-s)^4/t^4$$

$$+ cb_4(1 - s^4/t^4) + c^2 b_1 b_4 (t-s)^4/t^4]$$

and the age-specific relative risk for such an individual compared to a lifelong non-smoker of the same age, $R^s(s,t)$, is given by

$$R^s(s,t) = 1 + cb_1(t-s)^4/t^4 + cb_4(1 - s^4/t^4) + c^2 b_1 b_4 (t-s)^4/t^4.$$

By using a similar argument it can be shown that for an individual of age t who began to smoke cigarettes at the rate of c per day until stopping at age u, the age specific risk compared to a lifelong non-smoker, $R^s(s,u,t)$ is given by

$$R^s(s,u,t) = 1 + cb_1\{(t-s)^4 - (t-u)^4\}/t^4 + cb_4(u^4 - s^4)/t^4$$

$$+ c^2 b_1 b_4 (u-s)^4/t^4.$$

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LETTERS TO THE EDITOR

Lung cancer and passive smoking

Sir – Darby and Pike (1988; 58, 825) use a multistage model together with data on smoking and lung cancer to estimate the effect of exposure to other people's smoke on the risk of lung cancer. They give examples of the expected risks according to levels of passive smoking, expressed in terms of the number of equivalent cigarettes per day actively smoked.

In our review of the epidemiological studies of lung cancer and exposure to other people's tobacco smoke, we estimated that the risk of lung cancer among non-smokers living with smokers was about 50% higher than the risk in non-exposed non-smokers (Wald *et al.*, 1986). This risk, according to Darby and Pike, is approximately equivalent to smoking 0.5 cigarettes a day from birth to age 65 years, and they conclude it is some 5–17 times too high in the light of the level of biochemical markers of tobacco smoke exposure that have been measured in non-smokers. We did not think that this was so in our review and we are still of the opinion that the biochemical data are broadly in line with the estimates of risk based on epidemiological studies.

In our study of the principal marker, urinary cotinine (Wald *et al.*, 1984; Wald & Ritchie, 1984), the mean level in non-smokers who lived with smokers was about 1.5% (cited in Wald *et al.*, 1986; US National Academy of Science's Committee on Passive Smoking, 1986; Barlow & Wald, 1988) of the mean level found in active smokers, equivalent to smoking about 0.3 of a cigarette per day if active cigarette smokers typically smoke 20 cigarettes a day (1.5% of 20). An exposure equivalent to smoking 0.3 of a cigarette a day is similar to the estimate of 0.5 of a cigarette that would, according to the model adopted by Darby and Pike, 'explain' a 50% higher risk of having lung cancer in passive smokers. The half-life of serum cotinine in non-smokers may be about 50% greater than in smokers and, if this were the case, our estimate would become 0.2 instead of 0.3.

The principal reason for the difference in the estimates of Darby and Pike and our own arises from their use of data on urinary cotinine levels in passive smokers showing levels of 0.6–0.8% of active smokers (Jarvis *et al.*, 1984). We believe that the figure of 1.5% is more appropriate than that of Jarvis and his colleagues because they did not classify cotinine levels by the smoking habit of the person the subject lived with, which is needed when comparing the results with similar epidemiological data. They also excluded self-reported non-smokers with plasma cotinine levels greater than 20 ng ml^{-1}, which is likely to have excluded some individuals who, while not smokers themselves, were nonetheless heavily exposed to environmental tobacco smoke.

Bearing in mind the recognised uncertainties and difficulties involved in extrapolating from the biochemical data to the epidemiological data, there does not seem to be an obvious discrepancy between the two.

Yours etc.

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References

BARLOW, R.D. & WALD, N.J. (1988). Use of urinary cotinine to estimate exposure to tobacco smoke. *JAMA*, **259**, 1808.

JARVIS, M., TUNSTALL-PEDOE, H., FEYERABEND, C., VESEY, C. & SALLOOJEE, Y. (1984). Biochemical markers of smoke absorption and self reported exposure to passive smoking. *J. Epidemiol. Comm. Health*, **38**, 335.

NATIONAL RESEARCH COUNCIL (1986). *Environmental Tobacco Smoke. Measuring Exposures and Assessing Health Effects*. National Academy Press: Washington, DC.

WALD, N.J., BOREHAM, J., BAILEY, A., RITCHIE, C., HADDOW, J.E. & KNIGHT, G. (1984). Urinary cotinine as marker of breathing other people's tobacco smoke. *Lancet*, **i**, 230.

WALD, N.J., NANCHAHAL, K., THOMPSON, S.G. & CUCKLE, H.S. (1986). Does breathing other people's tobacco smoke cause lung cancer? *Br. Med. J.*, **293**, 1217.

WALD, N.J. & RITCHIE, C. (1984). Validation of studies on lung cancer in non-smokers married to smokers. *Lancet*, **i**, 1067.

Response to the letter from Dr. Wald

Sir – Wald and his colleagues question the conclusion we reached in our recent paper that there is a discrepancy between the low levels of exposure indicated by cotinine measurements in those passively exposed to cigarette smoke and the high relative risk for lung cancer of 1.5 from passive smoke exposure estimated by Wald *et al.* (1986) from epidemiological studies.

As noted by Wald and his colleagues, an important reason for the difference in our estimates is that we considered the urinary cotinine levels of passive smokers to be 0.6–0.8% that of active smokers, whereas they considered a figure of 1.5% to be more appropriate. Our figures were derived from Tables I and II of Jarvis *et al.* (1984). These data compared 27 non-smokers reporting 'some' or 'a lot' (there was no difference in the data from these two groups) of exposure to passive smoke to 94 smokers. The mean urinary cotinine for these 27 non-smokers reporting passive smoking exposure was 8.8 ng ml^{-1} while that for the smokers was 1,391.0, so that the ratio is 0.63% (8.8/1,391.0). A slightly higher figure is obtained if plasma and salivary values are considered, and for this reason we gave a range of 0.6–0.8%. In addition to these 27 non-smokers, there were 79 non-smokers with 'none' or 'a little' exposure to passive smoke, and 21 persons claiming to be non-smokers but whose level of plasma cotinine was according to the authors incompatible with their claim. Only one of the 100 accepted non-smokers (mean plasma cotinine, 1.5 ng ml^{-1}) had a plasma cotinine value above 10 ng ml^{-1} (actual value 14 ng ml^{-1}), whereas all the 21 'deceivers' had values above 20 ng ml^{-1} with a mean value of 239.3, which was 87% of the mean value for the declared smokers. Excluding those deceivers seems completely justified to us.

Taking, as do Wald and his colleagues, our high figure of 20 cigarettes per day consumption for smokers, and allowing a factor of 2/3 to account for the different half-life of cotinine in smokers and non-smokers, the cigarette equivalent exposure of passive smokers is estimated to be 2/3 × 0.63% of 20 cigarettes per day or 0.08, which is still only one-sixth

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of the lowest equivalent amount (0.5 cigarettes per day) that the multistage model predicts could cause a relative risk of 1.5. Clearly classification of cotinine levels by the smoking habit of the person with whom the subject lived might alter these figures, but we have been unable to find any data subdivided in this way in which efforts have also been made to exclude deceivers.

As we stated in our paper, it may simply be that cotinine is not an adequate measure of the exposure of non-smokers to the carcinogenic components of cigarette smoke. It is also possible that, given all the uncertainties and unknowns involved, in particular knowledge of the comparability of the passive smoke exposure of those in the lung cancer case–control studies to those in the surveys of Jarvis *et al.* (1984) and of Wald and Ritchie (1984), a factor of six is effectively good agreement. Careful studies may be able to resolve this issue.

Yours etc.

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References

JARVIS, M., TUNSTALL-PEDOE, H., FEYERABEND, C., VESBY, C. & SALLOOJEE, Y. (1984). Biochemical markers of smoke absorption and self reported exposure to passive smoking. *J. Epidemiol. Comm. Health*, **38**, 335.

WALD, N.J., NANCHAHAL, K., THOMPSON, S.G. & CUCKLE, H.S. (1986). Does breathing other people's tobacco smoke cause lung cancer? *Br. Med. J.*, **293**, 1217.

WALD, N.J. & RITCHIE, C. (1984). Validation of studies on lung cancer in non-smokers married to smokers. *Lancet*, **i**, 1067.

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ETS AND CANCER OF SITES OTHER THAN THE LUNG

Introduction

A presenter at the recent McGill Symposium in Montreal, Canada, described the then-available epidemiologic studies on ETS and cancer other than the lung as follows:

> These nine studies provide insufficient data to evaluate the effect of ETS on cancer other than of the lung. The reported associations are weak and inconsistent, and are subject to the potential effects of biases and uncontrolled confounding factors . . .[1]

These studies concern a variety of cancer sites; the publications on each are briefly summarized below. Highlighted copies of the papers on cancer at other sites are found at Tabs 1-11.

All Cancers Combined

- Several studies have presented risk estimates for overall cancer incidence, regardless of site, among individuals reporting ETS exposure. This procedure disregards differences in etiology, mechanism and confounding factors among the various types of cancer; nevertheless, some authors have presented data in this fashion.

Hirayama (1984) reported a significant elevation in risk for "cancer of all sites," in nonsmoking women whose husbands

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smoked; he attributed the elevation to increased risks for lung, nasal sinus, and brain cancers.[2]

Miller (1984) reports on a "case-control" study conducted in Pennsylvania by interviewing the surviving relatives of women whose death notices were published in a local newspaper.[3] Miller reported an overall odds ratio of 1.40 for "death due to cancer" among women whose husbands smoked. Questions can be asked about the accuracy of the amount of recall required of the relatives in this study.

In an abstract, Reynolds, et al., (1987) reported that a record-linkage study in Alameda County, CA concluded that nonsmoking women married to smokers had a 70% higher risk of cancer incidence at all sites, and that they had an approximate relative risk of 7.0 for "smoking-related cancers."[4] The abstract provides insufficient information to judge the quality of the study; the reported risk estimates should be viewed with caution.

Sandler, et al., (1989) reported statistically nonsignificant point estimates of 1.01 (males) and 1.00 (females) for all cancers in persons reporting ETS exposure.[5] The authors' subdivision of the category into "smoking-related" and "other" cancers yielded no statistically significant risk estimates. This study was criticized by Holcomb (1989) as being "poor science" and

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"inadequately designed."[6]

Brain and Nasal Sinus Cancers

- A single report claims to show an increased risk for brain and nasal sinus cancers associated with marriage to a smoker. No other researchers have been able to replicate these findings and they must be considered isolated.

Only Hirayama (1984), reporting further on his study of Japanese women, has reported statistically significant associations in women between brain and nasal sinus cancers and spousal smoking.[2]

Breast Cancer

- Some claims have been made for a relationship between husband's smoking and breast cancer in nonsmoking women.

Sandler, et al., (1985) reported a statistically non-significant increased risk for breast cancer in non-smoking women and statistically significant elevated risks for cancers of the endocrine system associated with early life (i.e., childhood) exposure to parental smoking.[7]

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Hirayama (1984), in his discussion of his claim that his data support an elevated risk for all cancers in nonsmoking women whose husbands smoke, suggested that part of the reported increase might be due to breast cancer.[2] In a 1991 article, Wells reports a statistically nonsignificant increased risk of breast cancer using additional data supplied by Hirayama.[8]

Bladder Cancer

- Two case-control studies have specifically examined bladder cancer incidence; neither reported an association between bladder cancer and exposure to ETS at home or at work.

The 1986 Kabat, et al., paper reported that cases and controls in this study did not differ significantly in reporting "sidestream smoke exposure" at home, at work or in transportation.[9] Neither did they differ significantly in whether or not their spouse smoked. The authors concluded that "exposure to sidestream smoke" is not an important factor in bladder cancer in nonsmokers.

The second study to report on bladder cancer is by Burch et al. (1989).[10] It was conducted in Alberta and Ontario, Canada. None of the reported relative risks was statistically significant. The authors concluded that there was no evidence for an effect of

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"passive smoking" on bladder cancer incidence in smokers or nonsmokers.

Cervical Cancer

- Two studies have reported on ETS exposure and the incidence of cervical cancer. Both fail to account sufficiently for confounding factors.

Statistically significant elevated risks for cervical cancer were reported in a 1985 study by Sandler, et al., of patients in North Carolina.[11] This study has been criticized because it did not control for known risk factors such as sexual activity, which is strongly correlated with incidence of cervical cancer.

Slattery, et al., (1989), in a study of women in Utah, reported a statistically significant increased risk of cervical cancer in non-smokers who reported three or more hours of ETS exposure per day (risk estimate of 3.43, 95% CI 1.23-9.54).[12] Although the researchers adjusted for age, church attendance, education and number of sexual partners, these variables do not account for all factors that may contribute to disease.

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Zang, Wynder and Harris authored a letter in response to the Slattery, et al., study.[13] They wrote:

> [T]here clearly is undermatching of control patients with regard to important risk factors including sexual activity, religious background, and education. . . . Since the previously mentioned risk factors are correlated highly with one another as well as with active and passive smoking, the risk estimates relating smoking and cervical cancer may be subject to substantial bias and confounding. . . . In fact, the adjusted odds ratios are probably no more than the leftover effect of variables controlled imperfectly by logistic regression.

In a response, Slattery acknowledged that her group's conclusions "should be verified in other studies."[14]

Childhood Cancers

- Two papers have claimed that their data show that childhood exposure to ETS is related to increased incidence of certain childhood cancers.

Grufferman, et al., (1982) reported a statistically significant relative risk of 3.9 (95% CI 1.5-9.6) for father's cigarette smoking for childhood rhabdomyosarcoma in a case-control study in North Carolina.[15] Only 33 cases were included in the study; only 23 cases were included in the analysis of father's smoking. Conversely, for the 8 cases with maternal smoking, the reported relative risk was 0.8 (95% CI 0.3-2.0). An extremely

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large number of analyses was conducted in this study, suggesting the possibility of data-dredging.

A recent study (John, et al., 1991) reported associations for father's smoking during pregnancy (i.e., a surrogate for ETS exposure of the pregnant woman) in the absence of maternal smoking, with several indices of childhood cancer: all cancers combined (OR = 1.2, 95% CI 0.8-2.1), acute lymphocytic leukemia (OR = 1.4, 95% CI 0.6-3.1), lymphomas (OR = 1.6, 95% CI 0.5-5.4) and brain cancer (OR = 1.6, 95% CI 0.7-3.5).[16] Not one of the associations was statistically significant.

Conclusion

- The studies concerning ETS exposure and cancer other than of the lung are few in number and subject to the same criticisms applicable to the lung cancer studies, e.g., "data-dredging," no assessment of exposure, inadequate control for confounding factors. Additionally, there are only one or two reports on a given cancer endpoint. Without replication of the results, it is not possible to reach any conclusion about ETS exposure and non-pulmonary cancer incidence.

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REFERENCES

1. Layard, M.W., "Environmental Tobacco Smoke and Cancer: The Epidemiologic Evidence," Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989, eds. D. Ecobichon and J. Wu, (Lexington, Massachusetts: Lexington Books, 1990): 99-115.

2. Hirayama, T., "Cancer Mortality in Nonsmoking Women with Smoking Husbands Based on a Large-Scale Cohort Study in Japan," Preventive Medicine 13: 680-690, 1984.

3. Miller, G.H., "Cancer, Passive Smoking and Nonemployed and Employed Wives," The Western Journal of Medicine 140: 632-635, 1984.

4. Reynolds, P., Kaplan, G.A. and Cohen, R.D., "Passive Smoking and Cancer Incidence: Prospective Evidence from the Alameda County Study," (abstract) American Journal of Epidemiology 126(4): 767, 1987.

5. Sandler, D.P., Comstock, G.W., Helsing, K.J. and Shore, D.L., "Deaths from All Causes in Non-Smokers Who Lived with Smokers," American Journal of Public Health 79: 163-167, 1989.

6. Holcomb, L.C., "Risk to Passive Smokers," (letter to the editor) American Journal of Public Health 79(10): 1432, 1989.

7. Sandler, D.P., Everson, R.B., Wilcox, A.J. and Browder, J.P., "Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking," American Journal of Public Health 75(5): 487-492, 1985.

8. Wells, A.J., "Breast Cancer, Cigarette Smoking, and Passive Smoking," (letter to the editor) American Journal of Epidemiology 133(2): 208-210, 1991.

9. Kabat, G.C., Dieck, G.S. and Wynder, E.L., "Bladder Cancer in Nonsmokers," Cancer 57: 362-367, 1986.

10. Burch, J.D., Rohan, T.E., Howe, G.R., Risch, H.A., Hill, G.B., Steele, R. and Miller, A.B., "Risk of Bladder Cancer by Source and Type of Tobacco Exposure: A Case-Control Study," International Journal of Cancer 44: 622-628, 1989.

11. Sandler, D.P., Everson, R.B. and Wilcox, A.J., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 121: 37-48, 1985.

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12. Slattery, M.L., Robison, L.M., Schuman, K.L., French, T.K., Abbott, T.M., Overall, J.C. and Gardner, J.W., "Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer," Journal of the American Medical Association 261: 1593-1598, 1989.

13. Zang, E.A., Wynder, E.L. and Harris, R.E., "Exposure to Cigarette Smoke and Cervical Cancer," (letter to the editor) Journal of the American Medical Association 262(4): 499, 1989.

14. Slattery, M.L., "Exposure to Cigarette Smoke and Cervical Cancer: In Reply," (letter to the editor) Journal of the American Medical Association 262(4): 499, 1989.

15. Grufferman, S., Wang, H.H., DeLong, E.R., Kimm, S.Y.S., Delzell, E.S. and Falletta, J.M., "Environmental Factors in the Etiology of Rhabdomyosarcoma in Childhood," Journal of the National Cancer Institute 68(1): 107-113, 1982.

16. John, E.M., Savitz, D.A. and Sandler, D.P., "Prenatal Exposure to Parents' Smoking and Childhood Cancer," American Journal of Epidemiology 133(2): 123-132, 1991.

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Cancer, Passive Smoking and Nonemployed and Employed Wives

G. H. MILLER, PhD, *Edinboro, Pennsylvania*

Passive smoking (inhalation by nonsmokers of tobacco smoke produced by smokers) as a cause of cancer is presently a topic of intense debate. Short-term passive smoking has long been associated with irritation of the eyes and allergic reactions,[1] although the overall effect was believed to be inconsequential. Passive smoking by children exposed in households of smoking parents has been shown in most studies to cause a two-fold increase in the incidence of pulmonary diseases.[1] Despite studies reporting high concentrations of various carcinogens in both main- and side-stream tobacco smoke,[2] the potential effect of passive smoking was considered negligible.

Only recently have the effects of long-term passive smoking (two or more decades of exposure) been studied. The first report of findings was published in 1978 by Miller.[3] This information was reported a year later at the Fourth World Conference on Smoking and Health in Stockholm.[4] Additional findings were reported by White and Froeb,[5] Hirayama,[6] Trichopoulos and co-workers[7] and Garfinkel.[8] Four of the five reports showed significant support for the hypothesis that passive smoking is associated with increased health risks, and one showed positive but nonsignificant results.

The present study was devised to investigate the health effects of long-term passive smoking on nonsmoking women by comparing a group of wives with little or no exposure with a group of wives with long-term exposure. The measurement of the effect of this exposure is by noting deaths from cancer. Because nonsmoking wives whose husbands also do not smoke may, nevertheless, be exposed to passive smoking in an out-of-the-home workplace, there is a problem of properly classifying passive smoking exposure. To investigate this potential out-of-the-home confounding factor, two comparisons of passive smoking were made—one including employed wives and one excluding employed wives.

Subjects and Methods

The Northwestern Pennsylvania Study of Smoking and Health (NPSSH) began in 1973 to gather data on the smoking habits of deceased persons in Erie County (Pennsylvania) by interviewing the deceased's next of kin. Death notices for the years 1972 through 1976 were obtained from the local newspaper, which lists the names of nearly all Erie County residents who have died and information on surviving relatives.

The 1970 Erie County population was 263,654, which includes Erie, the third largest city in Pennsylvania. The population of Erie County is primarily a middle-income group (the average family income for 1970 was listed as $9,380[9]) with a low migration rate (7%) for the 1950-1970 time period as reported by the Pennsylvania Department of Commerce.

Telephone numbers of one to three surviving relatives were obtained for each death notice whenever possible. Telephone numbers could not be located for about 15% of the cases due to factors such as no surviving relatives in Erie County, unlisted telephone numbers or the transient status of the deceased. Deaths due to accidents, suicides, congenital anomalies and in persons younger than 30 years of age were not included.

Construction of a questionnaire for the interviews was completed with the assistance of the local branches of the American Cancer Society, the American Heart Association and the American Lung Association and by members of the Pennsylvania Department of Health. A more detailed description of this questionnaire has been reported elsewhere.[10]

Interviewers explained the purpose of the study to the identified surviving relatives and solicited their cooperation. Information was collected on each deceased's cause of death, age, occupation (including information on whether or not the wife worked outside the home) and smoking history, as well as whether or not the spouse and parents smoked. The interviews were conducted by the director of the study and qualified interviewers trained by him. The questionnaire was revised in 1975 to obtain more complete information on a spouse's smoking habits such as type and quantity of tobacco used, the age of the spouse at the time of death or the current age if living, and the year or

(Miller GH: Cancer, passive smoking and nonemployed and employed wives. West J Med 1984 Apr; 140:632-635)

Presented at the Fifth World Conference on Smoking and Health, Winnipeg, Canada, July 11, 1983.

Reprint requests to G. H. Miller, PhD, Director, Studies on Smoking, 104 Valley View Drive, Edinboro, PA 16412.

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TABLE 1.—*Mean Age of Death By Cause of Death for Nonsmoking Women (Erie County, Pennsylvania), 1975-1976*

Group	Cause of Death Cancer	Number	Cause of Death Other Than Cancer	Number
All Women				
Smoking husband	67.58	89	75.33	270
Nonsmoking husband	70.58	34	82.95	144
Nonemployed Women*				
Smoking husband	68.56	66	76.62	238
Nonsmoking husband	71.72	18	84.12	126

*Does not work outside the home.

decade of death if deceased. These additional items permitted a more detailed analysis of the effects of passive smoking. Among the relatives contacted, 95% provided information for the study.

For the purposes of this study, a nonsmoker was considered to be one who had smoked fewer than 20 packs of cigarettes during his or her lifetime. An employed wife was identified by a surviving relative as a full-time employee in an occupation other than housework.

The most complete data were from the 1975-1976 interviews and therefore will be the only data considered in this report. A total of 4,130 deceased were located in the death notices for Erie County in the first 20 months of 1975 and 1976. Forms were completed for 3,288 of the deceased by the research assistants. A total of 842 deceased listed in the death notices were not included in the study for the following reasons:

No survivors in Erie County	685
Younger than 30 years of age	130
Accidents (listed in death notices)	27
TOTAL	842

The interviewers completed 1,838 interviews from the 3,288 completed forms. Information was not obtained for 1,450 deceased for the following reasons:

Lack of funds to complete interviews	1,091
Inability to locate relatives	292
Age younger than 30, accidents; refusals	67
TOTAL	1,450

A final total of 537 nonsmoking women was obtained from the 1,838 interviews after deleting the following categories:

Smoking men	825
Nonsmoking men	194
Smoking women	204
Single women	24
Insufficient information on passive smoking	54
TOTAL	1,301

To simplify problems of classification, husbands were considered nonsmokers if they satisfied the definition of not smoking more than 20 packs of cigarettes during their lifetime. All other persons classified as light smokers, moderate smokers, heavy smokers, former smokers and smoking husbands who died during any stages of the marriage were considered smokers. Although information was available for the different types of smoking classifications, a more detailed analysis would have provided subclassifications too small to make valid comparisons.

The nonsmoking wives were analyzed in the following ways:

- All wives
  - HNS—husbands did not smoke (no exposure)
  - HSM—husbands did smoke (long-term exposure)
- Excluding employed wives
  - XHNS—husbands did not smoke (wives did not work outside home)
  - XHSM—husbands did smoke (wives did not work outside home)

The data were analyzed in a manner appropriate for a retrospective case-control study.[11,12] The wives of smoking husbands and those of nonsmoking husbands were separated into the following categories by cause

TABLE 2.—*Causes of Death in All Women in Relation to Husbands' Smoking History*

Age Group Years	Husbands' Smoking Group	Deaths Due to Cancer Number	Deaths From Other Causes Number	Deaths Due to Cancer Percent	Odds Ratio	χ^2
80 and older	Smoker	14	150	0.09	1.28	0.27
	Nonsmoker	8	110	0.07		
70 to 79	Smoker	27	87	0.24	0.62	1.24
	Nonsmoker	11	22	0.33		
60 to 69	Smoker	22	20	0.52	0.40	1.99
	Nonsmoker	11	4	0.73		
59 and younger	Smoker	26	13	0.61	4.00	4.21*
	Nonsmoker	4	8	0.33		
TOTAL GROUP	Smoker	89	270	0.34	1.40	2.18
	Nonsmoker	34	144	0.19		
MEDIAN AGE	Smoker	68.0	81.0			
	Nonsmoker	71.8	83.4			

*This value is significant at the .05 level of significance.

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of death: those who died of any form of cancer, and those who died of any other cause.

The classification of the cause of death was based on the primary designation of death indicated by a surviving relative. Although a relative's classification may not be as accurate as a physician's in identifying the actual site of the original cancer, both are aware of whether or not the primary cause of death was due to cancer. There were only five deaths due to lung cancer reported in the entire group. The number was too small to provide stable results using standard statistical techniques; therefore, all causes of cancer were combined. This method thus avoids the problem of establishing the primary site.

Results

The mean age at death for the four groups listed above is given in Table 1. The odds ratio, percentage of deaths due to cancer and χ^2 analysis by age groups (aged 80 years and older, 70 to 79, 60 to 69, aged 59 years and younger and total for all age groups) are reported for the HNS and HSM groups in Table 2 and for the XHNS and XHSM groups in Table 3. Table 4 has similar data for women working outside the home; however, χ^2 analysis was not completed due to the small sample size.

Table 2 (all wives) shows a highly positive but not statistically significant association between long-term passive smoking and cancer as a cause of death for the entire group. The odds ratio is 1.40 and the χ^2 value is 2.18 (P .15) for all wives.

When women working outside the home are omitted (Table 3), the odds ratio increases to 1.94, which is statistically significant ($P<.02$). Thus, long-term passive smoking appears to nearly double the risk of death

TABLE 3.—*Cause of Death in Nonemployed Wives* in Relation to Husbands' Smoking History*

Age Group Years	Husbands' Smoking Group	Deaths Due to Cancer Number	Deaths From Other Causes Number	Deaths Due to Cancer Percent	Odds Ratio	χ^2
80 and older	Smoker	11	145	7.1	1.93	1.35
	Nonsmoker	4	102	3.8		
70 to 79	Smoker	22	72	23.4	0.61	0.99
	Nonsmoker	8	16	33.3		
60 to 69	Smoker	16	11	59.2	1.94	0.61
	Nonsmoker	3	4	42.8		
59 and younger	Smoker	17	10	63.0	2.27	0.93
	Nonsmoker	3	4	42.8		
Total Group ..	Smoker	66	238	21.7	1.94	5.441
	Nonsmoker	18	126	12.5		
Median Age ...	Smoker	69.5	81.9			
	Nonsmoker	75.0	83.9			

*Does not work outside the home.
†Significant at $P = .05$.

TABLE 4.—*Cause of Death in Wives Who Worked Outside the Home in Relation to Husbands' Smoking History*

Age Group Years	Husbands' Smoking Group	Deaths Due to Cancer Number	Deaths From Other Causes Number	Deaths Due to Cancer Percent	Odds Ratio
80 and older	Smoker	3	5	37.5	1.2
	Nonsmoker	4	8	33.3	
70 to 79	Smoker	5	15	20.0	0.66
	Nonsmoker	3	6	33.3	
60 to 69	Smoker	6	9	40.0	...
	Nonsmoker	8	0	100.0	
59 and younger	Smoker	9	3	75.0	12.0
	Nonsmoker	1	4	20.0	
Total Group ..	Smoker	23	32	41.9	0.80
	Nonsmoker	16	18	47.1	
Median Age ...	Smoker	65	73.3		
	Nonsmoker	69	75.0		

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from cancer for nonsmoking women with smoking husbands compared with nonsmoking women with nonsmoking husbands.

The proportion of cancer deaths in this Erie County group (excluding confounding factors such as persons younger than 30 years and traumatic deaths) was 22.9%, which is comparable to the 22.68% for the national average reported by the American Cancer Society.[13]

When wives who work outside the home are included, the odds ratio for the aged 59 years and younger group is high and the result is statistically significant (P .05). When this category of wives is excluded, the odds ratios for all age groups other than the 70-to-79-years age groups are 1.93 or higher.

Discussion

The results of the study provide support for the hypothesis that long-term passive smoking leads to excess cancer deaths in exposed nonsmokers.

This conclusion is based on the almost twofold increase in the mortality due to cancer among nonemployed wives who had long-term exposure to passive smoking compared with nonemployed wives with little or no exposure.

The suspicion that wives who work outside the home are exposed to a different environment is supported by the somewhat different results in Tables 2 and 3. For employed wives, the fact that the husbands smoked or did not smoke seems to be unimportant (Table 4). Instead of the non-smoke-contaminated air of a household in which both spouses are nonsmokers, a nonsmoking wife may find herself breathing smoke and other hazards in a workplace. Clerks, secretaries, teachers, nurses and factory workers are among those who may be exposed to carcinogens in work areas or lounges.

This confounding factor of working outside the home with respect to passive smoking and other potential pollutants can explain the differences in the results reported in the studies of Hirayama, Trichopoulos and associates, and the study of Garfinkel. The Hirayama study took place in Japan and the Trichopoulos study in Greece. In both of these countries there are fewer wives working outside the home. Nonemployed wives in these countries are likely to have little contact with tobacco smoke outside the home. The large American Cancer Society sample that was originally reported by Hammond[14] was the data base for the Garfinkel study. This sample was from a relatively more affluent social class likely to contain many women who worked or volunteered outside the home.

Because the Hirayama and Trichopoulos studies had a negligible number of employed wives in their sample, comparisons were made between relatively "pure," nonexposed groups and long-term exposed groups for an analysis of passive smoking. The Garfinkel report, on the other hand, included partially exposed nonsmoking women in the so-called nonexposed groups, thus reducing any potential difference between his two groups. This difference in the composition among the groups being compared is a likely explanation of why the Hirayama and Trichopoulos studies and the present study (with employed wives excluded) show a twofold to threefold increase in mortality from cancer associated with long-term passive smoking, whereas the Garfinkel study shows a smaller but still positive relative risk.

The odds ratio in Table 2 in which wives working outside the home are included is 1.40. The Garfinkel study reports a value of 1.37 for the mortality ratio of wives exposed to tobacco smoke from husbands who smoked less than a pack a day. Although one must be cautious in comparing the odds ratio and the mortality ratio, the similarity cannot be disregarded.

The significant difference reported in Table 2 for the group aged 59 years and younger derives from a fourfold increase in relative risk related to passive smoking. While this might appear to be high, an analysis of the same age group for husbands engaged in agriculture in the detailed Hirayama data[15] gave a similar result—that is, the mortality ratio of wives whose husbands smoked is 3.63 times greater than that of the nonexposed wives. This value is similar to the Erie County result. Whereas the data from this study show borderline significance for the effect of passive smoking and cancer, an analysis of Tables 2 and 3 shows high odds ratios in the lower age categories and small cell values. Therefore, the data base should be increased to determine whether or not these trends continue with a larger population sample.

Additional properly designed studies are necessary on the hazards of passive smoking. Nevertheless, the data now available indicate that the best policy for a nonsmoking person should be to avoid exposure to tobacco smoke whenever possible.

REFERENCES

1. The Health Consequences of Smoking: The Surgeon General's Report. US Dept of Health, Education, and Welfare publication No. (HSM) 72-7516. Government Printing Office, 1972, pp 119-138
2. Smoking and Health. The Surgeon General's Report. US DHEW publication No. (PHS) 79-50066. Government Printing Office, 1979
3. Miller GH: The Pennsylvania Study on Passive Smoking. J Breath Ill Lung Assoc 1978, 41:5-9
4. Abstracts—Fourth World Conference on Smoking and Health, Stockholm, Sweden, September 20, 1979
5. White JR, Froeb HF: Small-airways dysfunction in nonsmokers chronically exposed to tobacco smoke. N Engl J Med 1980, 302:720-723
6. Hirayama T: Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. Br Med J 1981 Jan, 282:183-185
7. Trichopoulos D, Kalandidi A, Sparros L, et al: Lung cancer and passive smoking. Int J Cancer 1981 Jan, 27:1-4
8. Garfinkel L: Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. JNCI 1981 Jun, 66:1061-1066
9. County and City Data Book 1972—A Statistical Abstract Supplement. US Dept of Commerce, 1972, p 551
10. Miller GH: Smoking and longevity. J Breath Ill Lung Assoc 1976; 39:3-13
11. Fleiss JL: Statistical Methods for Rates and Proportions. New York, Wiley, 1973, pp 53-66
12. Hayden GF, Kramer MS, Horwitz RI: The case control study—A practical review for the clinician. JAMA 1982, 247:326-331
13. American Cancer Society: Cancer statistics, 1982. CA 1982; 32: 13-19
14. Hammond EC: Smoking in relation to the death rate of one million men and women. In Haenszel W (Ed): Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. JNCI Monogr 1966; 19:127-204
15. Hirayama T: Nonsmoking wives of heavy smokers have a higher risk of lung cancer. Br Med J 1981, 283:916-917

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Proceedings of the Society for Epidemiologic Research[1]

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ABSTRACTS OF PAPERS PRESENTED AT THE TWENTIETH ANNUAL MEETING OF THE

Society for Epidemiologic Research

Amherst, Massachusetts
June 17–19, 1987

CONTRIBUTED PAPERS
Cancer I
Chairman: V. Ernster

Human papilloma virus infection and cervical neoplasia in Greenland and Denmark. S. K. Kjaer,* O. M. Jensen, E. M. deVillier, and H. Zur Hausen (Danish Cancer Registry, 2100 Copenhagen, Denmark).

The incidence of cervical cancer in Greenland is four times higher than in Denmark. Reasons for this were studied in 584 Greenlandic women and 660 Danish women aged 20–39 years. The women were drawn at random from the population of Nuuk, Greenland and Nykobing, Denmark. Human papilloma virus infection (measured by hybridization of cervical deoxyribonucleic acid (DNA)) and other known or suspected risk factors for cancer of cervix uteri (determined from questionnaire, cervical smear, and blood samples) were investigated. Human papilloma virus 16/18 infection was associated with an increased relative risk (RR) of dysplastic cells (RR = 2.7; 95% confidence interval = 1.2–6.1) which was similar in Greenland (RR = 2.4) and Denmark (RR = 3.2). Surprisingly, the prevalence of human papilloma virus 16/18 infection was lower in Greenland (8.7%) than in Denmark (12.5%), $p = 0.028$. As anticipated, the Greenlandic women exhibited characteristics of a high-risk population for cervical cancer compared with the Danish women, e.g., less than 17 years at first intercourse, 84% vs. 45%; 25 or more sexual partners, 41% vs. 1%; current smokers, 87% vs. 53%; and herpes simplex virus type 2, 68% vs. 31%. This large population-based study thus gives support to the association between human papilloma virus 16/18 and cervical neoplasia; however, the relative risk is much lower than previously predicted from clinical series. Furthermore, the difference in cervical cancer incidence between Greenland and Denmark seems to be determined by risk factors other than human papilloma virus 16/18 infection.

Familial ovarian cancer: a population-based case-control study. J. Schildkraut* and W. D. Thompson (Yale U. School of Medicine, New Haven, CT 06510).

Data from a multi-center population-based case-control study were analyzed in order to assess the degree of aggregation of ovarian cancer in families. Included as cases were 493 women, ages 20–54 years, who had been newly diagnosed with epithelial ovarian cancer. The frequency with which cases reported a family history of ovarian cancer was compared with the frequency for a group of 2,454 controls selected by random digit dialing. The odds ratios for ovarian cancer in first- and second-degree relatives were, respectively, 3.6 (95% confidence interval (CI) = 1.8–7.1) and 2.9 (95% CI = 1.6–5.3). The null hypothesis of no association was excluded on both the maternal and paternal sides of the families studied. Ovarian cancer in relatives was reported significantly more frequently by women with malignant lesions than by women with borderline lesions. These results seemed attributable neither to the possible confounding effects of several covariates nor to errors in reporting family history of ovarian cancer. This is the largest controlled study to date of familial aggregation of ovarian cancer and is the only one to compare borderline and malignant tumors with respect to family history.

Risk factors for endometrial cancer; a case-control study. S. M. Lesko,* L. Rosenberg, D. W. Kaufman, and S. Shapiro (Slone Epidemiology Unit, Brookline, MA 02146).

The risk of endometrial cancer in relation to various reproductive and medical history factors was evaluated in a hospital-based case-control study of 526 women with endometrial cancer (cases) and 965 women with other diseases (controls). The rate ratio (RR) estimate for body mass index of 30+ kg/m^2 relative to body mass index <30 kg/m^2, adjusting for other relevant factors, was 3.7 (95% confidence interval (CI) = 2.5–5.5). Endometrial cancer risk was somewhat elevated for women with a history of diabetes (RR = 1.5, 95% CI = 0.9–2.7) or hypertension (RR = 1.5, 95% CI = 1.1–2.2). The estimate for late age at menopause (55 years or older), relative to menopause which occurred before age 45 years, was 2.0 (95% CI = 0.8–4.5); for high parity (5+ pregnancies), relative to nulliparity, the risk was reduced (RR = 0.6, 95% CI

* Indicates person who delivered the paper.

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Case-control study of dietary cholesterol and lung cancer. M. T. Goodman,* L. N. Kolonel, J. H. Hankin, and C. Yoshizawa (Cancer Research Center of Hawaii, Honolulu, HI 96813).

There are few reports of any lung cancer-cholesterol association in the literature. To pursue the finding of a strong, positive correlation between dietary cholesterol intake and lung cancer incidence among 10 ethnic-sex groups in Hawaii, the authors gathered interview data from a population-based series of lung cancer cases (298 men and 122 women) and a group of matched population controls (697 men and 271 women). Nutrient information was obtained by the diet history method with the use of a personal interview. Both the frequency and quantity of consumption of approximately 127 food items were assessed. Among men, the odds ratio for lung cancer by quartiles of dietary cholesterol consumption (lowest intake to highest intake) were 1.0, 1.9, 1.7, and 2.2 after adjustment for age, ethnicity, pack-years of cigarette use, and intake of dietary carotene (p for trend, <0.01). The association of dietary cholesterol intake with the risk of lung cancer was strongest for men with squamous cell cancer, although there was also an increased risk for adenocarcinoma of the lung associated with the highest percentiles of consumption. No effect of cholesterol on the development of lung cancer was found among women. The relation of dietary fat intake to lung cancer was also explored, and a positive association was found with total, saturated, and unsaturated fat. However, because of the high correlation between dietary fat and cholesterol ($r = 0.7$), it was difficult to distinguish between the independent effects of these nutrients on the risk of lung cancer.

A cohort study on cancer mortality among residents in a chronic arseniciam *endemic* area. R. Lin* (College of Medicine, National Taiwan U., Taipei, Taiwan).

In a limited area on the southwest coast of Taiwan where artesian well water with a high content of arsenic has been consumed for more than 45 years, chronic arsenicism manifested by skin lesions and peripheral vascular disease among residents has been well-documented. In addition to skin cancer, lung and liver cancers were also found to be highly prevalent in the endemic area. A retrospective cohort study on mortality among inhabitants of three fishing villages in a semi-isolated location in this area was conducted. A total population of 4,694 persons from 768 families registered in household records in 1946 was traced up to 1985. The death certificates of 845 residents who died between 1966 and 1985 at age 40 years and over were collected from vital records. A total of 333 persons (39.4%) died from cancer, and of these 333 persons, 93 (28%) had urothelial cancers, which include cancers of the bladder, kidney, and ureter. Males and females were equally affected. As compared with an expected number of 1.8 deaths from urothelial cancer, a 50-fold increased risk was found among these residents. The findings suggested that arsenic or other carcinogens in the artesian well water may be associated with the pathogenesis of urothelial cancer.

Cancer II
Chairman: E. Ron

Acute nonlymphocytic leukemia and allergies. R. Severson,* R. Stevens, D. Thomas, S. Davis, L. Heuser, and L. Sever (Kuakini Medical Center, Honolulu, HI 96817).

Epidemiologic evidence suggests that the immune system plays a role in the development of leukemia. Persons with immunodeficiency diseases or autoimmune conditions and persons treated with alkylating agents (which are immunosuppressants) are at increased risk of leukemia. On the other hand, there is some suggestion that people with allergies are at decreased risk of leukemia, but, to date, few studies have been reported. The association between allergies and adult acute nonlymphocytic leukemia was examined in a population-based case-control study of 114 cases and 133 controls. Cases were identified through a cancer registry in Seattle, Washington, and the controls were randomly selected from the population by random digit dialing. Prior allergy was associated with a significantly decreased risk of adult acute nonlymphocytic leukemia which was accounted for primarily by acute myelocytic leukemia (odds ratio = 0.35, 95% confidence interval = 0.2–0.6). Risk of acute myelocytic leukemia declined with increasing number of prior allergies (trend, $p < 0.001$). This association was consistent across specific allergies with a decreased acute myelocytic leukemia risk identified for 13 separate allergies.

Risk factors for anal and rectal squamous cell carcinoma. E. A. Holly,* A. W. Whittemore, S. Chiu, J. Kristiansen, and D. Aston (Northern California Cancer Center, Belmont, CA 94002–5030).

A case-control study was conducted to determine whether a relation existed between anal or rectal squamous cell and cloacogenic carcinoma, and sexual practices, sexually transmitted diseases, or treatment for these diseases. Preliminary analyses have begun on data on 111 patients and 326 randomly selected controls. A history of homosexual experiences was reported by 41% of all male cases and 9% of male controls. These differences yielded an estimated relative risk of 13.3 (95% confidence interval = 5.0–35.3). Male cases and controls differed significantly with respect to drug use, tobacco use, sexually transmitted diseases, anal intercourse, and anal fissures, with relative risks ranging from 2.1 to 27.0. However, several of these characteristics were positively correlated with homosexual life-style. Female cases and controls differed significantly with respect to anal fissures, smoking, and anal intercourse, with relative risks ranging from 1.3 to 2.9. Results of multivariate analyses are presented with control for confounding variables.

Case-control study of in utero and postnatal exposures in childhood acute nonlymphoblastic leukemia. L. Robison,* J. Buckley, A. Daigle, M. Nesbit, D. Arthur, W. Woods, R. Wells, L. Odom, and D. Hammond (Children's Cancer Study Group, Pasadena, CA 91101).

To assess specific in utero and postnatal exposures,

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and H. Abbey (The Johns Hopkins U. School of Hygiene and Public Health, Baltimore, MD 21205).

A nested case-control study, which used serum collected in 1974 in Washington County, Maryland, compared serum levels of androgens and vitamins among 30 cases of prostate cancer diagnosed between 1980 and 1985 and 42 controls of similar age, sex, and race. Mean levels of androgens were slightly higher among cases than controls, with respective testosterone levels of 417 and 379 ng/dl ($p = 0.25$) and dihydrotestosterone levels of 63.4 and 54.1 ng/dl ($p = 0.09$). Odds ratios for cancer risk associated with androgen levels above the median values were 2.74 for testosterone (95% confidence interval (CI) = 0.99–7.61) and 1.31 for dihydrotestosterone (95% CI = 0.51–3.35). Mean levels of retinol, beta-carotene, lycopene, and vitamin E showed only trivial differences between cases and controls. However, interactions were observed between testosterone and retinol, lycopene, and vitamin E. At high vitamin levels, high levels of testosterone were not associated with increased risk of prostate cancer, whereas at low vitamin levels, the risk associated with high level of testosterone was considerably increased (six- to eightfold). The degree of interaction remained essentially the same after adjustment for the effect of cigarette smoking and education. These findings suggest that these vitamins may be important in the etiology of prostate cancer.

Passive smoking and cancer incidence: prospective evidence from the Alameda County Study. P. Reynolds* (California Dept. of Health Services, Emeryville, CA 94608), G. A. Kaplan, and R. D. Cohen.

The association between the smoking habits of spouses and subsequent cancer incidence was explored in a cohort of 2,413 married women (46% of whom were never smokers) who participated in a 1965 population-based survey in Alameda County, California. Smoking history was independently ascertained for each spouse. Cancer incidence was assessed via automated record linkage to the population-based cancer registry that has served Alameda County since 1960. During the 17-year follow-up period, the women in the study contributed 19,323 person-years of observation, and 147 were diagnosed with cancer (38 with smoking-related cancers). The risk relation was analyzed using Cox proportional hazards modeling. Women who were nonsmokers and whose husbands smoked were at 70% higher risk of cancer incidence ($p = 0.035$) for all sites compared with women whose husbands did not smoke. For smoking-related cancers, the approximate relative risk was 7.0 ($p = 0.09$). The evidence was equivocal for an effect of passive smoking in women who had ever smoked.

A molecular biologic study of bovine leukemia virus in childhood acute lymphoblastic leukemia and non-Hodgkin's lymphoma. A. Bender* (Minnesota Dept. of Health, Minneapolis, MN 55440), L. Robison, S. Kashmiri, W. Woods, K. McClain, A. Smithson, R. Heyn, J. Finlay, L. Schuman, and R. Gibson.

Bovine leukemia virus is the causative agent of enzootic bovine lymphosarcoma and is highly infectious to cattle and sheep. Much speculation continues to be directed at the role of bovine leukemia virus in human leukemia. To rigorously test this hypothesis, the authors conducted a case-control study of childhood acute lymphoblastic leukemia/non-Hodgkin's lymphoma between December 1983 and February 1986. Cases (less than age 16 years at diagnosis) were derived from patients diagnosed at the primary institutions and affiliate hospitals; 196 cases (112 males and 84 females) were identified, and age-, sex-, race-matched regional population controls were selected. In-person interviews were conducted with parents of cases and controls. In addition, bone marrow/peripheral blood from 157 cases (131 acute lymphoblastic leukemia cases and 26 non-Hodgkin's lymphoma cases) and peripheral blood from 136 controls were studied. Case samples were obtained prior to treatment. Samples from all subjects were shipped within 24 hours to a central laboratory. Deoxyribonucleic acid (DNA) was extracted by standard methods, digested with EcoRI, electrophoresed in agarose gel, and hybridized with bovine leukemia virus cloned probe under highly stringent conditions by Southern blot analysis. None of the 157 case or 136 control DNA samples demonstrated bovine leukemia virus. The high statistical power and specificity of this study provide the best evidence to date that genomic integration of bovine leukemia virus is not a factor in childhood acute lymphoblastic leukemia/non-Hodgkin's lymphoma.

Is cigarette smoking a stronger risk factor for lung cancer mortality for women than for men? Evidence from a cohort study with follow-up into the 1980s. B. A. Cohn,* D. L. Wingard, P. M. Cirillo, R. D. Cohen, and G. A. Kaplan (Human Population Laboratory, Berkeley, CA 94704).

The authors examined whether smoking is a stronger risk factor for lung cancer mortality for women than for men in a sample of 5,239 persons representative of Alameda County, California, who were followed for mortality during 1965–1983. In a Cox model, adjusted for age, pack-years was a stronger predictor for women. The relative hazard (20 pack-years vs. none) for women was 1.8 times that for men ($p = 0.02$). In addition, the sex ratio for lung cancer mortality varied significantly by age, with the greatest male excess among those aged 50–69 years at entry and declining in older groups. Among those under age 50 years at entry, lung cancer mortality rates were greater for females than for males. The pack-years-sex and the age-sex interactions were independent of each other. Sex differences in lung cancer mortality could not be simply explained by sex differences in lifetime smoking. The burden of lung cancer mortality for female smokers may be even greater than that experienced by male smokers.

POSTER SESSIONS I
Chairman: D. Mundt

Occupational exposures of parents of children with acute nonlymphocytic leukemia. J. D. Buckley, L. L. Robison, D. Arthur, A. Daigle, M. Nesbit, W. Woods, L. Odom, R. Wells, J. Peters, R. Swotinsky, and D. Hammond (Children's Cancer Study Group, Pasadena, CA 91101).

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Deaths from All Causes in Non-Smokers Who Lived with Smokers

DALE P. SANDLER, PHD, GEORGE W. COMSTOCK, MD, DRPH, KNUD J. HELSING, SCD, AND DAVID L. SHORE, PHD

Abstract: Mortality associated with passive smoking was evaluated in a 12-year study of 27,891 White adult smokers and 19,035 never smokers identified in 1963. Death rates were calculated using an estimate of the person-years at risk. **Adjusted for age, marital status, education, and quality of housing, the estimated relative risks of death from all causes were 1.17 (approximate 95% confidence interval 1.01, 1.36) for men and 1.15 (1.06, 1.24) for women with passive exposure.** These relative risks were similar to those for ex-smokers and for pipe or cigar smokers. Risks increased slightly with level of exposure. **The relative risk from passive smoking was greatest for men under age 50 (RR = 2.09, 1.31–3.34).** Risks from passive smoking were slightly elevated for several causes among men and women, and may be broader than those previously reported. On the other hand, these small nonspecific increases in death rates may reflect other characteristics of passive smokers that increase mortality. (*Am J Public Health* 1989; 79:163–167.)

Introduction

Smokers are generally reported to have almost doubled age-adjusted death rates.[1] This increased mortality is observed for all causes combined as well as for specific causes, and is not entirely explained by smokers' substantially increased risk for lung cancer or arteriosclerotic heart disease.

Non-smokers who live with smokers are exposed to many of the same potentially toxic consituents of cigarette smoke[2] and they, too, may be at increased risk for death from a variety of causes. These "passive smokers," like active smokers, have increased levels of smoke by-products in body fluids,[3,4] increased activation of enzyme systems that metabolize potential carcinogens,[5] and increased levels of urinary mutagens,[6,7] albeit all at much lower levels than active smokers.

More than a dozen studies have demonstrated increased lung cancer risk among passive smokers,[2] and several studies have suggested increased heart disease risk for passive smokers.[8–11] Studies have also reported increased overall cancer risk,[12–14] with risks not limited to respiratory tract cancers, but the data are limited and findings inconclusive. Only a few reports have concerned total mortality among passive smokers. In the Multiple Risk Factor Intervention Trial, total mortality was increased nearly two-fold among men at risk for heart disease who were married to smokers.[8] A small increase in total mortality was reported for non-smoking women with environmental tobacco smoke exposure in Scotland, but no association was observed for men.[15] Total mortality was slightly increased for passively exposed women in a small US study,[9] but no association between passive smoke exposure and total mortality was found in a study in Amsterdam.[16]

We evaluated mortality from all causes and specific causes in non-smokers living with smokers who had been surveyed in 1963 as part of a private community-wide census in Western Maryland.

Methods

In July 1963 a private census obtained data on an estimated 98 per cent of the households in Washington County, Maryland. The census provided information on sex, age, race, marital status, years of schooling, church attendance, and housing characteristics for 91,909 individuals. Information on cigarette, cigar, and pipe smoking habits was recorded for each household member age 16-½ or older as of July 15, 1963.

To take into account losses from the population resulting from deaths and emigration, a follow-up study of a 5 per cent sample of households that took part in the 1963 census was conducted in 1971. Age, marital status, years of schooling, and frequency of church attendance were associated with remaining in the county after eight years based on a linear model that adjusted for effects of these and other socioeconomic and demographic variables. The addition of sex, smoking status in 1963, and number of bathrooms to the model did not alter the results. The resulting linear model was used to assign to each adult in the 1963 census their probability of still living in the county. From this, an annual probability could be calculated, allowing the population remaining in the county to be estimated at any point in time. The procedure used to estimate the probability of remaining in the county has been described in greater detail by Comstock and Tonascia.[17]

Death certificates of Washington County residents who died between July 1963 and July 1975 were matched against the census and have been coded by one of the authors (GWC) as to primary, contributing, and underlying causes of death according to the seventh revision of the International Classification of Disease (ICD).[18] For this report, deaths were classified in broad groupings using the underlying cause of death.

Data are reported here for adults who were over age 25 in 1963. Because only about 2 per cent of the census population was Black, the analysis is limited to Whites. This report is based on data from a total of 22,973 White men and 25,369 White women.

Study subjects were classified according to their smoking status in 1963. Smoking status was not known for 587 men (2.6 per cent) and 527 women (2.1 per cent). An additional 212 men and 90 women known to be smokers were excluded from this report because the number of cigarettes smoked was not known, leaving 22,174 men and 24,752 women for analysis.

A household smoke exposure score was calculated to serve as a measure of passive smoking. To create this score, each adult was assigned a smoking contribution score ranging from 0 to 12 based on their personal smoking history.[11] A household smoking total was calculated as the sum of the smoking contribution scores of all persons living in that household, and each individual's household smoke exposure

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TABLE 1—All Cause Mortality by Smoking Status in 1963

Smoking Status	Men				Women			
	N#	Deaths	Adj RR*	(95% CI)	N#	Deaths	Adj RR*	(95% CI)
Non-smokers	2,914	585	1.00	—	5,322	1,224	1.00	—
Passive smokers	1,248	258	1.17	(1.01, 1.36)	9,551	1,556	1.15	(1.06, 1.24)
Pipe/cigar only	1,671	504	1.20	(1.07, 1.35)	10	2	0.70	(0.18, 2.75)
Ex-smokers	4,562	997	1.16	(1.05, 1.28)	2,153	186	1.03	(0.87, 1.21)
Current smokers	11,779	2,090	1.41	(1.29, 1.55)	7,716	697	1.26	(1.13, 1.40)
<10 cigarettes	1,583	315	1.14	(0.99, 1.31)	2,248	222	1.12	(0.96, 1.30)
10+ cigarettes	10,196	1,775	1.49	(1.35, 1.64)	5,468	475	1.34	(1.19, 1.52)

Number of subjects
*Adjusted for age, housing quality, schooling, and marital status.

score was the household total minus his or her own contribution to it. The person's own smoking was treated separately in the analysis.

The household exposure score cannot measure total passive smoke exposure because it is not known, for example, how many of the cigarettes smoked per day were smoked outside of the home. Nevertheless, this score is an indicator of the relative degree of exposure in 1963. The group of non-smokers living with non-smokers will have had, on average, the least household exposure to tobacco smoke, while persons living with several heavy smokers will have had, on average, the highest levels of household exposure. Among the 4,162 men and 14,873 women who were reported in 1963 as never smokers, 1,248 men (30.0 per cent) and 9,551 women (64.2 per cent) had household smoke exposure and are considered passive smokers; the remainder are considered non-smokers.

A housing index (ranging from 0 to 10) based on running water, number of bathrooms, type of heating system, cooking fuel, and availability of a telephone was created to serve as a rough indicator of quality of housing and socioeconomic status. For this analysis, housing quality has been classified as poor (index = 0–7) or good (index = 8–10). Education has been categorized as 0–8, 9–11, 12, and 13 or more years of schooling. Subjects were characterized as those married in 1963 and those not. In overall analyses, age has been categorized as 25–44, 45–54, 55–64, and 65+. In analyses restricted to those under age 50, age was categorized as less than 40 and 40–49 in 1963. For persons older than 50, age was categorized as 50–59, 60–69, and 70 or more years.

Average annual death rates were calculated as the number of deaths during the 12 years from 1963 to 1975 divided by the number of person-years of follow-up estimated from the assigned probability scores for still living in the county. Relative risks were calculated as the average annual death rates among smokers or passive smokers divided by the death rates among nonsmokers without household smoke exposure. Age, marital status, and other factors were strongly related to both death rates and smoking status in this population. Accordingly, all relative risks were adjusted for differences in age, marital status, housing quality, and education using Poisson regression.[19]

Results

The number of deaths and person years of follow-up are shown by smoking status in 1963 and sex in Table 1. After adjusting for age, marital status, education, and housing quality, passive smokers were at increased risk for death from all causes relative to non-smokers. Adjusted relative risks were 1.17 (approximate 95 per cent confidence intervals 1.01, 1.36) for men and 1.15 (1.06, 1.24) for women. These relative risks were similar to those for pipe or cigar smokers, ex-smokers, and smokers of fewer than 10 cigarettes a day, and were less than half that observed for heavier active smokers.

Among men, the relative risk for passive smokers under age 50 was 2.09 (1.31, 3.34), and the relative risk for heavier active smokers was 3.16 (2.27, 4.41) (Table 2). Among those age 50 and older, the corresponding relative risks were substantially less. The difference between the death rates for passive smokers and non-smokers was similar, however, in both age groups (2.6/1,000 for those younger than age 50 and 2.3 for those 50 and older). Among women, while the relative risk for active smoking was greater for those younger than 50 in 1963, the relative risk for passive smoking did not vary with age. Among passive smokers there was some increase in

TABLE 2—All Cause Mortality by Smoking Status and Age in 1963

Smoking Status	Men				Women			
	Age <50		Age 50+		Age <50		Age 50+	
	Adj RR*	(95% CI)	Adj RR	(95% CI)	Adj RR	(95% CI)	Adj RR	(95% CI)
Non-smokers	1.00	—	1.00	—	1.00	—	1.00	—
Passive smokers	2.09	(1.31, 3.34)	1.11	(0.95, 1.30)	1.14	(0.81, 1.62)	1.14	(1.05, 1.23)
Pipe/cigar only	1.83	(1.13, 2.96)	1.13	(1.00, 1.28)	—	—	0.72	(0.18, 2.86)
Ex-smokers	1.94	(1.34, 2.81)	1.15	(1.03, 1.28)	1.57	(1.05, 2.36)	1.00	(0.83, 1.20)
Current smokers	3.06	(2.20, 4.27)	1.33	(1.20, 1.47)	1.79	(1.30, 2.47)	1.27	(1.13, 1.43)
<10 cigarettes	2.28	(1.49, 3.48)	1.12	(0.97, 1.30)	1.34	(0.88, 2.02)	1.18	(1.00, 1.39)
10+ cigarettes	3.16	(2.27, 4.41)	1.39	(1.26, 1.55)	1.96	(1.42, 2.71)	1.33	(1.16, 1.53)

*Adjusted for age, housing quality, schooling, and marital status.

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TABLE 3—All Cause Mortality among Never Smokers by Degree of Passive Smoke Exposure and Age

Exposure Score	Age <50 Deaths	Age <50 Adj RR*	Age <50 (95% CI)	Age 50+ Deaths	Age 50+ Adj RR	Age 50+ (95% CI)	Total Deaths	Total Adj RR	Total (95% CI)
Men									
0 (none)	37	1.00	—	548	1.00	—	585	1.00	—
1+ (any)	35	2.09	(1.31, 3.34)	223	1.11	(0.95, 1.30)	258	1.17	(1.01, 1.36)
1–5 (light)	12	1.59	(0.83, 3.07)	95	1.11	(0.89, 1.38)	107	1.13	(0.92, 1.39)
6+ (heavy)	23	2.50	(1.48, 4.24)	128	1.11	(0.91, 1.35)	151	1.20	(1.00, 1.44)
Women									
0	47	1.00	—	1,177	1.00	—	1,224	1.00	—
1+	132	1.14	(0.81, 1.62)	1,424	1.14	(1.05, 1.23)	1,556	1.15	(1.06, 1.24)
1–5	53	1.24	(0.83, 1.86)	650	1.09	(0.98, 1.21)	703	1.12	(1.02, 1.24)
6+	79	1.08	(0.75, 1.58)	774	1.17	(1.06, 1.28)	853	1.16	(1.06, 1.27)

*Adjusted for age, housing quality, schooling, and marital status.

overall relative risk for death from all causes with increasing household exposure to smoke, but no clear trends (Table 3).

Passive smoking-associated adjusted relative risks for individual causes of death are shown for never smoking men and women in Table 4. The relative risks for male and female passive smokers were greater than one for several smoking related and other causes, although risk estimates were stable only for arteriosclerotic heart disease in men and for arteriosclerotic heart disease, cerebrovascular disease, and chronic lung disease in women.

There were few deaths among men younger than 50 in 1963, but the relative risks for several causes of death, including arteriosclerotic heart disease and cancer, were greater than 2.00 (data not shown).

The increased relative risk for chronic lung disease among women with smoke exposure was limited to women over age 50 in 1963; there were no deaths in this category among younger women. The risk for cerebrovascular disease did not differ by age, but cancer risk was increased only among women younger than age 50. **All 12 "smoking-related" cancers (two lung, five cervix, one kidney, three pancreas) among never smoking women younger than 50 were in those with passive smoke exposure.**

Among the never smokers, 44 per cent of the deaths among men and 35 per cent of the deaths among women were attributed to arteriosclerotic heart disease. After excluding these deaths, there continued to be an increase in overall mortality for women with passive smoke exposure (Table 5). For men, mortality from causes other than arteriosclerotic heart disease was increased only among passive smokers younger than age 50 [RR = 1.93 (1.09, 3.41)].

Discussion

The finding of increased overall mortality for non-smokers who lived with smokers may not reflect a causal relationship. Much of the increased risk we observed could be attributed to arteriosclerotic heart disease for which an extensive literature documents an increased risk associated with active cigarette smoking.[20] Our own study[11] and others have demonstrated increased risk for heart disease in passive smokers. Svendsen, *et al*,[8] reported non-smoking men married to smokers were at increased risk for heart disease death [RR = 2.11 (0.69, 6.46)] and risk increased with amount smoked by the spouse. Hirayama[10] reported a 20 per cent increase in mortality from ischemic heart disease among non-smoking women married to smokers. Heart disease

TABLE 4—Deaths from all Causes and Specific Causes among Never Smoking Men and Women

Cause of Death	Men Deaths: Passive Smokers (12,238 PY)	Men Deaths: Non-smokers (29,214 PY)	Men Adj RR*	Men (95% CI)	Women Deaths: Passive Smokers (97,032 PY)	Women Deaths: Non-smokers (51,113 PY)	Women Adj RR	Women (95% CI)
All causes	258	585	1.17	(1.01, 1.36)	1,556	1,224	1.15	(1.06, 1.24)
Cancer	31	84	1.01	(0.66, 1.53)	290	211	1.00	(0.82, 1.21)
Smoking related	8	24	0.96	(0.43, 2.16)	49	27	1.45	(0.88, 2.40)
Other	23	60	1.03	(0.40, 2.62)	241	184	0.93	(0.76, 1.54)
Cerebrovascular disease	33	93	0.97	(0.65, 1.46)	297	232	1.24	(1.03, 1.49)
Circulatory diseases	137	304	1.19	(0.97, 1.46)	715	576	1.17	(1.05, 1.32)
Arteriosclerotic heart disease	122	248	1.31	(1.05, 1.64)	551	437	1.19	(1.04, 1.36)
Other	15	56	0.65	(0.36, 1.18)	164	139	1.14	(0.89, 1.29)
Respiratory diseases	15	27	1.44	(0.75, 2.75)	79	72	1.21	(0.87, 1.69)
Emphysema/Bronchitis	2	4	0.93	(0.16, 5.32)	11	2	5.65	(1.19, 26.8)
Other	13	23	1.53	(0.76, 3.07)	68	70	1.08	(0.76, 1.54)
Digestive diseases	9	18	1.34	(0.59, 3.04)	57	39	1.20	(0.78, 1.85)
Genitourinary diseases	3	12	0.67	(0.36, 1.28)	21	11	1.50	(0.69, 3.26)
Accidental causes	15	24	1.48	(0.78, 2.84)	48	35	1.24	(0.78, 1.30)
Other	15	23	1.70	(0.88, 3.29)	49	48	0.76	(0.50, 1.17)

*Adjusted for age, housing quality, schooling, and marital status.

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TABLE 5—Mortality among Never Smokers from Arteriosclerotic Heart Disease and Other Causes

Cause of Death	Men		Women	
	Adj RR*	(95% CI)	Adj RR	(95% CI)
Arteriosclerotic heart disease	1.31	(1.05, 1.64)	1.19	(1.04, 1.36)
Other causes	1.06	(0.87, 1.31)	1.12	(1.02, 1.24)

*Adjusted for age, housing quality, schooling, and marital status.

mortality associated with passive smoking was also increased in studies reported by Gillis, *et al*,[15] and by Garland, *et al*,[9] but risk estimates were based on small numbers. A study reported by Lee, *et al*,[21] indicated no heart disease risk from passive smoking.

In our study, an increased relative risk for death remained even after subtracting deaths from arteriosclerotic heart disease. The effect was strongest for women and for younger men. The general increase in mortality leaves open the possibility that the life styles of people who live with smokers differ from those who do not live with smokers. Factors such as alcohol consumption or dietary habits which are correlated with both smoking and risk for some diseases (and which were not collected in the 1963 census) seem especially likely to be alternative explanations for our findings, to the extent that diets or alcohol use are similar among household members.

Studies of passive smokers in general and of passive smokers with heart disease have also examined some of these potential confounding factors with mixed results. In 1963, more than 60 per cent of never smoking women in Washington County lived with smokers,* but it was much less common for non-smoking men to live with smokers. Differences between these men and other men might explain their slight increase in overall mortality. Never smokers who lived with smokers had fewer years of schooling and lived in housing of poorer quality. We adjusted for these differences in our analysis, but residual confounding might still affect our results.

Others have found few differences between those with and without passive smoke exposure that could account for mortality differences between groups. Garland, *et al*,[9] found no difference in blood pressure, obesity, or cholesterol between women married to smokers and those married to never smokers. Svendsen, *et al*,[8] found no differences in blood pressure, cholesterol, or psychosocial factors between men married to smokers and men married to non-smokers. They did, however, find that men married to smokers were slightly heavier and drank alcoholic beverages slightly more often than those married to non-smokers. Similarly, Friedman, *et al*,[22] reported that alcohol consumption and other risk-taking behaviors were more frequent among non-smokers with passive smoke exposure.

Besides heart disease, several other causes of death for which we observed increased death rates for passive smokers are causes that are known or suspected to be caused in part by cigarette smoke. These include respiratory diseases such as emphysema and bronchitis[23] and cerebrovascular disease.[24,25]

Kalandidi, *et al*,[26] recently reported in a case-control study that non-smoking women married to current smokers had nearly twice the risk of lung disease as did non-smoking women married to never smokers. Increased chronic lung disease mortality was also reported by Hirayama[27] for Japanese women married to smokers (RR = 1.4), but results in the study by Lee, *et al*,[21] were inconclusive. Two studies also included data on risk of cerebrovascular disease. Based on very small numbers, stroke risk was increased for women with environmental tobacco smoke exposure in the study by Gillis, *et al*.[15] In the study by Lee, *et al*,[21] stroke mortality was increased approximately two-fold for both men and women with high total passive smoke exposure, although not in relation to spouse smoking alone.

While lifestyle or selection factors are a possible explanation for the small increase in overall mortality we observed, it is also possible that continued exposure to cigarette smoke leads to poorer health in general. Smokers have more respiratory illnesses and decreased lung function relative to non-smokers.[24] They may also have altered immune system responses and other changes which indirectly affect disease risk and response.[1] It is possible that passive smoke exposure indirectly increases overall mortality by altering general health status and increasing case-fatality from other illnesses. Increased respiratory symptoms and decreased lung function have been observed for passively exposed children and adults,[2] although not all studies have been positive.[28]

Finally, with relative risks as low as those observed here, and with such a weak dose-response, one must consider that other biases are responsible for these findings. The confidence intervals for the risk estimates shown do not take into account the variability associated with the estimated person years at risk. These estimates were derived from fitting a linear model to follow-up data obtained for a 5 per cent sample of the population. The true person-years of follow up may be larger or smaller than that calculated. Therefore the reported confidence intervals may be slightly too small.

Misclassification of smoking status is also possible. Smoking status was obtained once in 1963 as part of a general community census. Some persons classified as non-smokers may have taken up smoking in the years between 1963 and 1975, and non-smokers who lived with smokers may be more apt to become smokers. Similarly, non-smokers with no smoke exposure may have become exposed as other family members began to smoke or as household composition changed. However, it is more likely that active smokers became ex-smokers over the 12-year period, reducing the overall level of household smoke exposure at which these effects were observed. Thus the dose-specific effects may even be underestimated. Furthermore, individuals who were not exposed at home may have had smoke exposure at work, making it difficult to detect smoking-related health differences between groups.

*Sandler DP, Helsing KJ, Comstock GW, Shore DL: Factors associated with past household exposure to tobacco smoke. Submitted for publication.

REFERENCES

1. US Department of Health and Human Services: Smoking and Health: A Report of the Surgeon General. DHEW Pub No (PHS) 79–50066. Washington, DC: Govt Printing Office, 1979.
2. National Research Council: Environmental Tobacco Smoke—Measuring Exposures and Assessing Health Effects. Washington, DC: National Academy Press, 1986.
3. Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Salloojee Y: Biochemical markers of smoke absorption and self-reported exposure to passive smoking. J Epidemiol Community Health 1984; 38:335–339.
4. Wald NJ, Boreham J, Bailey A, Ritchie C, Haddow JE, Knight G: Urinary cotinine as marker of breathing other people's tobacco smoke. Lancet 1984; 1:230–231.

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5. Manchester DK, Jacoby EH: Sensitivity of human placental monooxygenase activity to maternal smoking. Clin Pharmacol Ther 1981; 30:687–692.
6. Bos RP, Theuws JLG, Henderson PTH: Excretion of mutagens in human urine after passive smoking. Cancer Lett 1983; 19:85–90.
7. Lofroth G, Lazaridis G: Environmental tobacco smoke: Comparative characterization by mutagenicity assays of sidestream and mainstream cigarette smoke. Environ Mutagen 1986; 8:693–704.
8. Svendsen KH, Kuller LH, Martin MJ, Ockene JK: Effects of passive smoking in the Multiple Risk Factor Intervention Trial. Am J Epidemiol 1987; 126:783–795.
9. Garland C, Barrett-Connor E, Suarez L, Criqui MH, Wingard DL: Effects of passive smoking on ischemic heart disease mortality of nonsmokers: A prospective study. Am J Epidemiol 1985; 121:645–650.
10. Hirayama T: Passive smoking—A new target of epidemiology. Tokai J Exp Clin Med 1985; 10:287–293.
11. Helsing KJ, Sandler DP, Comstock GW, Chee E: Heart disease mortality in nonsmokers living with smokers. Am J Epidemiol 1988; 127:915–922.
12. Hirayama T: Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 1984; 13: 680–690.
13. Sandler DP, Everson RB, Wilcox AJ: Passive smoking in adulthood and cancer risk. Am J Epidemiol 1985; 121:37–48.
14. Reynolds P, Kaplan GA, Cohen RD: Passive smoking and cancer incidence: prospective evidence from the Alameda County Study. Am J Epidemiol 1987; 126:767 (abstract).
15. Gillis CR, Hole DJ, Hawthorne VM, Boyle P: The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Respir Dis 1984; 65(suppl 133):121–126.
16. Vandenbroucke JP, Verheesen JHH, DeBruin A, Mauritz BJ, Van Der Heide-Wessel C, Van Der Heide RM: Active and passive smoking in married couples: Results of 25 year follow up. Br Med J 1984; 288:1801–1802.
17. Comstock GW, Tonascia JA: Education and mortality in Washington County, Maryland. J Health Soc Behav 1977; 18:54–61.
18. World Health Organization: Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. Vol 1. Based on the recommendations of the seventh revision conference, 1955. Geneva: WHO, 1957.
19. Frome EL, Checkoway H: Use of Poisson regression models in estimating incidence rates and ratios. Am J Epidemiol 1985; 121:309–323.
20. US Department of Health and Human Services: The Health Consequences of Smoking—Cardiovascular Disease: A report of the Surgeon General. DHHS Pub No (PHS) 84–50204. Washington, DC: Govt Printing Office, 1983.
21. Lee PN, Chamberlain J, Alderson MR: Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 1986; 54:97–105.
22. Friedman GD, Petitti DB, Bawol RD: Prevalence and correlates of passive smoking. Am J Public Health 1983; 73:401–405.
23. US Department of Health and Human Services: The Health Consequences of Smoking—Chronic Obstructive Lung Disease: A report of the Surgeon General. DHHS Pub. No. (PHS) 84–50205. Washington, DC: Govt Printing Office, 1984.
24. Abbott RD, Yin Y, Reed DM, Yano K: Risk of stroke in male cigarette smokers. N Engl J Med 1986; 315:717–720.
25. Colditz GA, Bonita R, Stampfer MJ, Willett WC, Rosner B, Speizer FE, Hennekens CH: Cigarette smoking and risk of stroke in middle-aged women. N Engl J Med 1988; 318:937–941.
26. Kalandidi A, Trichopoulos D, Hatzakis A, Tzannes S, Saracci R: Passive smoking and chronic obstructive lung disease. Lancet 1987; 2:1325–1326.
27. Hirayama T: Passive smoking and lung cancer, nasal sinus cancer, brain tumor and ischemic heart disease. Proceedings of the Fifth World Conference on Smoking and Health, Winnipeg, Canada, July 1983.
28. Comstock GW, Meyer MB, Helsing KJ, Tockman MS: Respiratory effects of household exposures to tobacco smoke and gas cooking. Am Rev Respir Dis 1981; 124:134–148.

NIDA Announces Availability of Videotapes on Drugs in the Workplace

The National Institute on Drug Abuse, the federal agency which serves as the focal point for research and demonstration programs on drug abuse, has announced availability of *Drugs at Work* and *Getting Help*—the first two in a four-part videotape series on drug abuse in the workplace. The videotapes are available either on free loan or for purchase.

- *Drugs At Work*, a 23-minute educational documentary, describes costs of drug use for the workplace, the individual, and the public, and examines action being taken by government and private companies. An important program for all levels in the workplace, from top management to line staff, *Drugs at Work* provides information for developing effective drug abuse workplace programs through policy development, drug testing, employee assistance programs, prevention, and education. Interviews are included with drug users who have sought treatment and with experts on drugs in the workplace. Government and industry representatives describe current federal and corporate programs.
- *Getting Help* presents detailed information about the use of Employee Assistance Programs (EAPs) in addressing drug use in the workplace. The film features comments by business, labor, and government leaders, and EAP professionals; presentation of three model programs; and EAP client interviews. It encourages employers to consider EAPs as a tool in combatting drugs at work, and provides employees with reassuring information about the confidentiality and effectiveness of an EAP program.

The third in the series, *Drug Testing*, and the fourth, *Drug Prevention and Employee Education*, will be available in the near future.

The videotapes—available in both employer and employee versions—are designed to be part of a comprehensive workplace drug abuse program. To arrange a free loan, contact: Modern Talking Picture Service Scheduling Center, 5000 Park Street, North, St. Petersburg, FL 33709, (813) 541-5763. To purchase, contact: National Audio Visual Center, Customer Service Section, 8700 Edgeworth Drive, Capital Heights, MD 20743–3701, (301) 763–1896.

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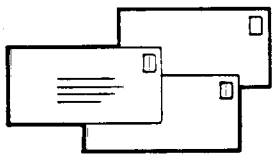

Letters to the Editor

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Letters should be submitted in duplicate, double-spaced (including references), and should not exceed 400 words.

Risk to Passive Smokers

Sandler[1] is a follow-up to an earlier publication by Helsing.[2] It raises issues that are in need of a response. These papers are a result of a 1963 survey in Maryland where health-related questions were asked, including smoking status. In 1975, death records were reviewed to determine if "passive smokers" were at more risk than nonsmokers who were not exposed to environmental tobacco smoke (ETS) in the home.

The introduction indicates the authors were conducting an "evaluation" of the population in question. However, there is no clear statement of the purpose of the investigation or definition of a problem.

The 1988 Helsing paper[2] reported a higher relative risk (1.31 for men and 1.24 for women) for deaths due to arteriosclerotic heart disease nonsmokers married to smokers versus nonsmokers married to nonsmokers. The Sandler study[1] reports a higher relative risk of death from all causes in ETS-exposed persons: 1.17 for men and 1.15 for women. The authors[1] admit the results could be influenced by confounding factors such as different lifestyle, including alcohol consumption in those in the group exposed to ETS. "Finally, with relative risks as low as those observed here, and with such weak dose-response, one must consider that other biases are responsible for these findings."

Significantly, Sandler fails to acknowledge the serious deficiencies and limitations of death certificates, his principal source of data. This could easily confound the intent of the study especially in those cases where death was the result of a terminal malignancy which was not confirmed by autopsy/histology.

Examination of Table 4 indicates another problem that could be termed "selective weighting" of population components. The paper ultimately draws attention to respiratory diseases data in this table. Examination of these numbers shows them to be very limited. The small sample size precludes effective and meaningful statistical evaluation.

Sandler[1] fails to recognize the 1988 report on lifestyle factors by Koo[3] that demonstrates confounding factors present in such evaluations of ETS. The reviews of epidemiological flaws as pointed out by Uberla with regard to ETS studies and by Feinstein[5] with regard to faulty methodology used in epidemiological studies in general are also ignored.

Overall, the Sandler[1] paper should have been rejected for publication on the basis that it is poor science and inadequately designed and undertaken to address the issue presented in the title. It adds little if anything to the body of data needed to allow a justifiable determination of the relationship between exposure to ETS and risk of mortality.

REFERENCES

1. Sandler DP, Comstock GW, Helsing KJ, Shore DL: Deaths from all causes in nonsmokers who lived with smokers. Am J Public Health 1989; 79:163–167.
2. Helsing KJ, Sandler DP, Comstock GW, Chee E: Heart disease mortality in nonsmokers living with smokers. Am J Epidemiology 1988; 127:915–922.
3. Koo LC, Ho JH, Rylander R: Life-history correlates of environmental tobacco smoke: A study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. Soc Sci Med 1988; 26:751–760.
4. Uberla K: Lung cancer from passive smoking: hypotheses or convincing evidence? Int Arch Occup Environ Health 1987; 59:421–437.
5. Feinstein, AR: Scientific standards in epidemiologic studies of the menace of daily life. Science 1988; 242:1257–1263.

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Response from Sandler and Comstock

In his letter, Holcomb has alleged serious deficiencies in our paper[1] on mortality in nonsmokers who lived with smokers. He wrote that because we "evaluated" mortality in nonsmokers living with smokers, we had no clear purpose in conducting our study. To the contrary, the study was designed specifically to obtain evidence bearing on possible health effects associated with living with smokers. We did not collect independent data for this purpose, but selected data from several existing sources that would best address this question. We do not claim to have a definitive test of our hypothesis and feel that our results have been appropriately qualified.

With respect to Holcomb's denigration of death certificate information, few will join him in challenging their usefulness in ascertaining total mortality in this or other developed countries. Death certificates do have limitations with respect to causes of death, and especially other conditions present at death. These limitations have rarely, however, misled the scientific world in searches for associations.

We reported that the overall death rate for nonsmokers who lived with smokers was increased relative to that for nonsmokers who were not exposed.[1] Certainly, Holcomb would agree that a death certificate indicates that a death has occurred. Helsing, *et al.*[2] clearly demonstrated an association between deaths attributed to arteriosclerotic heart disease and exposure to household tobacco smoke. Others will have to judge whether or not the association is causal in nature. Current evidence suggests causality as more likely than confounding. While Holcomb's attention was drawn to findings regarding respiratory diseases, this was not so singled out by us. Nonetheless, such an effect is consistent with what is known about smoking and lung disease.[3]

As we stated in our paper, we took advantage of data that had been collected for other purposes. For this rea-

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son we were not able to rule out alternative explanations for our findings to the extent we would have liked. We found few differences, however, in our study[4] or in other reports[5,6] that would account for our findings. Koo, *et al*,[7] compared 70 nonsmoking women with nonsmoking husbands to 66 nonsmoking women whose husbands smoked. They were able to shed very little additional light on the question of differences between smoking and nonsmoking households. In fact, many of the differences they observed, such as increased respiratory illnesses, use of medications and medical procedures, and adverse pregnancy outcomes, were likely to have been the result of living with smokers rather than an indication of fundamental differences between the groups.

We believe the findings of our study were worthy of publication. The study raises the possibility that living with smokers may have lasting detrimental effects on health. We hope our findings will encourage additional studies and serious dialogue about this issue.

REFERENCES

1. Sandler DP, Comstock GW, Helsing KJ, Shore DL: Deaths from all causes in nonsmokers who lived with smokers. Am J Public Health 1989; 79:163–167.
2. Helsing KJ, Sandler DP, Comstock GW, Chee E: Heart disease mortality in nonsmokers living with smokers. Am J Epidemiol 1988; 127:915–922.
3. US Department of Health and Human Services: The Health Consequences of Smoking—Chronic Obstructive Lung Disease: A report of the Surgeon General. DHHS Pub. No. (PHS)84-50205. Washington, DC: Govt Printing Office, 1984.
4. Sandler DP, Helsing KJ, Comstock GW, Shore DL: Factors associated with past household exposure to tobacco smoke. Am J Epidemiol 1989; 129:380–387.
5. Garland C, Barrett-Connor E, Suarez L, Criqui MH, Wingard DL: Effects of passive smoking on ischemic heart disease mortality of nonsmokers: A prospective study. Am J Epidemiol 1985; 121:645–650.
6. Svendsen KH, Kuller LH, Martin MJ, Ockene JK: Effects of passive smoking in the Multiple Risk Factor Intervention Trial: Am J Epidemiol 1987; 126:783–795.
7. Koo LC, Ho JH-C, Rylander R: Life-history correlates of environmental tobacco smoke: A study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. Soc Sci Med 1988; 26:751–760.

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Environmental Tobacco Smoke and Legal Issues

The Byrd, *et al*, review article[1] attempts to form a bridge between medical data pertaining to environmental tobacco smoke (ETS) and legal issues evolving from regulation of ETS. This bridge is needed to improve our understanding and management of ETS in ambient air.

To provide a scientific basis for their position, these authors must relate ETS exposure to a medical condition. They must define the causative agent. They must identify the route of exposure including concentration. There must be an exposure duration. If these are lacking, the resulting conclusions are compromised. This article considers the chemical composition of ETS merely by a discussion of chemical differences between mainstream and sidestream smoke.

When actual human ETS exposures are considered, this review article does not say much about typical concentrations of chemical constituents to which nonsmokers are exposed. Therefore, we never know the human dosage of any chemical constituent in ETS. There is no consideration of duration of exposure. All ETS studies performed to this date suffer from the absence of a reliable measurement of ETS exposure. Unfortunately, these authors ignore this research problem as well.

The Byrd, *et al*, review suggests that ETS causes respiratory distress in children, lung cancer, and cardiovascular/respiratory health problems. The children's studies are presented without mentioning the ambiguity of many results, the presence of confounding factors, and the subject stress introduced by the study procedures.

The Surgeon General's 1986 report[2] calls ETS a "plausible" cause of lung cancer which is accepted by this review. However, this review does not adequately communicate the conclusions in the body of the Surgeon General's 1986 report wherein much of the supporting research was found to be technically flawed and/or statistically insignificant. These authors also neglect to consider the psychological factors involved in the onset of cardiovascular/respiratory distress.

The literature review in this article is limited and slanted toward the political/personal opinions of the Surgeon General. The evaluation of medical data is brief and does not present the current status of science in this field. Consequently, this effort to link ETS medical data to evolution of legal thought is less than it should be. The remainder of the review is a historical treatment of legal/policy decisions which have addressed ETS.

ETS investigators will benefit from the overview of experienced scientists who apply empirical skills to this bridge area when they write review articles that are comprehensive and objective. The literature is presently overloaded with subjective manipulations of questionable data by review article authors, public health officials, and editors.

REFERENCES

1. Byrd JC, Shapiro RS, Schiedermayer DL: Passive smoking: A review of medical and legal issues. (Public Health & the Law) Am J Public Health 1989; 79:209–215.
2. US Department of Health and Human Services: The Health Consequences of Involuntary Smoking. A report of the Surgeon General. No. (CDC)87-8309. Washington, DC: Govt Printing Office, 1986.

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Response from Dr. Byrd

Dr. Halfen raises a number of important issues. The scientific study of passive smoking is barely a decade old. Much future research is necessary to resolve areas of uncertainty. Reliable information needs to be gathered on the fate of environmental tobacco smoke (ETS) in ordinary indoor environments; improved surveys quantifying passive smoke exposure should be developed; and biological studies must be refined to quantify the exposure-dose relationship in nonsmokers.

We disagree, however, with Dr. Halfen's assertion that a specific etiologic chemical needs to be identified in order to establish ETS as a cause of disease. Active cigarette smoking was known to cause lung cancer years before the chemical constituents of tobacco smoke were delineated. Now passive smoking has been shown to cause lung cancer. The goals of future research are to further define the magnitude of the risk and to seek the specific causative agents.

The investigation of passive smoking has become increasingly sophisticated. Recent studies have utilized more rigorous designs and monitoring

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Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking

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Abstract: We obtained data on smoking by parents from 438 cancer cases and 470 controls to investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke. Cancer cases were between ages 15 and 59 at time of diagnosis. All sites but basal cell cancer of the skin were included. Cancer risk was increased 50 per cent among offspring of men who smoked. Increased risk associated with father's smoking was not explained by demographic factors, social class, or individual smoking habits, and was not limited to known smoking related sites.

Relative risk (RR) estimates associated with father's smoking tended to be greatest for smokers, males, and non-Whites. There was only a slight increase in overall cancer risk associated with maternal smoking. Mother's and father's smoking were both associated with risk for hematopoietic cancers, and a dose-response relationship was seen. The RR for hematopoietic cancers increased from 1.7 when one parent smoked to 4.6 when both parents smoked. Although they should be considered tentative, study findings suggest a long-term hazard from transplacental or childhood passive exposure to cigarette smoke. (*Am J Public Health* 1985; 75:487–492.)

Introduction

Cancer risk in adult life may be affected by transplacental and childhood exposure to cigarette smoke.[1] Data from studies in animals have demonstrated that many carcinogens are active when administered transplacentally or during early life. In some instances, effects may be produced at lower doses than are required for adults.[2–4] The tumors resulting from these transplacental and early postnatal exposures may not be apparent until adulthood.[5,7–9]

Studies in humans demonstrate that the fetus of smoking parents is exposed to components of cigarette smoke and is capable of bioactivating these chemicals.[10–20] For example, cotinine has been measured in the amniotic fluid of smokers and passive smokers[13] and thiocyanate has been measured in fetal cord blood.[14–16] Studies have also demonstrated increased activity of enzymes that metabolize benzo(a)pyrene in placentas of women who smoke,[17–19] and possibly even in placentas of women passively exposed to cigarette smoke.[20] Similar elevations may occur in the tissues of the fetus or exposed child. Finally, increased urinary excretion of mutagens has been found in passive smokers.[21]

Several epidemiologic studies have demonstrated increased risk for childhood tumors in relation to either paternal or maternal smoking,[22–24] but not all studies demonstrate an increased risk.[25,26] Even if no increased risk of childhood cancer were found, however, it would not rule out the possibility of increased cancer risk during adult life from fetal or childhood exposure. One recent study found elevated lung cancer risk for individuals whose mothers smoked.[27]

Cigarette smoke contains many known carcinogens.[28] Sidestream smoke, which is the smoke released from the cigarette between active puffs, may differ qualitatively from the mainstream smoke which is inhaled by the active smoker.[28] Some compounds occur in markedly higher concentrations in sidestream smoke, and although this smoke is diluted by the ambient air into which it is released, the passive smoker may inhale smoke which is qualitatively richer in certain compounds than mainstream smoke (Hoffman in 28). For example, the concentration of dimethylnitrosamine in sidestream smoke is 52 times that in mainstream smoke. Such qualitative differences make it difficult to predict the biologic effect of exposure to sidestream smoke.

In this study we investigate whether cancer risk in adult life is related to transplacental or childhood exposure to cigarette smoke.

Methods

Our study methods have been described in greater detail elsewhere.[29] Cancer cases were selected from the hospital based tumor registry at the North Carolina Memorial Hospital of the University of North Carolina in Chapel Hill. They included all cases diagnosed between July 1, 1979 and March 31, 1981 and assumed to be alive as of March 31, 1981. Cases were between ages 15 and 59 at time of diagnosis and included all cancer sites except basal cell cancer of the skin. Cases were restricted to age 59 and younger, since fewer than 5 per cent of women of child bearing age in 1920 were smokers.[30,31]

Cases were mailed a questionnaire for self completion, followed by a second mailing and a telephone call if needed. Of 740 eligible cancer cases identified from the tumor registry, 107 (14 per cent) died before we could contact them. An additional 115 (16 per cent) either refused (n = 71) to participate or could not be contacted. Cases who died or did not respond were slightly older and were more often male or non-White; cases with respiratory cancer were more likely to have been excluded, presumably due to higher case fatality. In all, completed questionnaires were obtained for 518 (70 per cent) of the eligible cases.

In addition to questions on exposure to cigarette smoke, cases were asked to identify friends or acquaintances who did not have cancer and were the same race, sex, and age (± 5 years) to serve as comparison subjects. Approximately 60 per cent of the controls were identified in this manner. For cases for whom friend controls were not successfully obtained, population controls were identified by systematic telephone sampling. Data were analyzed separately by control selection group and the adjusted results were nearly identical to those obtained when the control groups were combined.

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Individuals were specifically requested to supply information on natural parents. Only individuals who lived with both natural parents for all or most of the first 10 years of life are included in this report. As a result, 128 individuals were excluded (80 cases and 48 controls).

Transplacental and childhood exposure to cigarette smoke was assessed from questionnaire reports of smoking histories of parents. Subjects were asked whether parents ever smoked, smoked before the subject's birth, smoked in the house for most of the years before the subject was 10 years old, and whether mothers smoked while pregnant with the study subject. Subjects were also asked the usual quantity of cigarettes smoked by the parents and the frequency of smoking in the house. For this report, unless otherwise specified, exposure is classified by parental smoking in the household before the subject attained 10 years of age.

For this report, "smoking related" tumors were defined as cancer of the oral cavity and pharynx, esophagus, pancreas, respiratory and intrathoracic organs, urinary tract and cervix.[25] Because evidence linking cervical cancer with cigarette smoking is not well documented, we also analyzed these data with cervical cancer excluded from this designation. The number of "smoking related" tumors was substantially reduced by this exclusion, but the general findings were not altered. For individual smoking status, smokers are defined to include anyone who ever smoked at least one cigarette a day for as long as six months. Nonsmokers are individuals who have never smoked.

Estimates of the relative risk (RR) in stratified analyses were obtained using the Mantel-Haenszel technique[32] for the summary odds ratio. The method of Gart[33] was used to obtain 95 per cent confidence limits for the combined estimates of RR. Estimates of the relative risk adjusted simultaneously for multiple confounding variables were obtained using a multiple logistic model.

Level of education was reported as number of years of school completed and occupation was given as usual occupation. For stratified analyses, age and level of education were treated as categorical variables with four levels of age (<30, 30–39, 40–49, 50+) and three levels of education (<12 years, 12 years, >12 years). Age was treated as a continuous variable in the multiple logistic analysis.

Controls were matched one-to-one to cases to allow the selection of population controls without having an enumerated sampling frame. The analyses presented here are unmatched to maximize the study size following losses due to missing data on exposure. In most comparisons, the factors used in control selection are taken into account by adjustment procedures. Analyses using matched pairs gave similar results.

Results

Cases and controls are distributed similarly by age, race, and sex (Table 1). Cases and controls differ only in their distribution by years of schooling with fewer cases having completed high school. However, cases and controls are similar in broad occupational categories. Cases and controls are similar with regard to their own smoking status with 45 per cent of cases and 47 per cent of controls never having smoked; the similarity is largely due to the use of friends as controls. When only cases with population controls are included, 57 per cent of cases and 47 per cent of population controls were smokers.

Maternal Smoking

There was only a small difference between cases and controls in reported exposure to maternal smoking [estimated relative risk (RR) = 1.1, 95 per cent confidence limits = 0.7, 1.6]. The RR for cancer among individuals whose mothers smoked was close to one for all measures of maternal smoking, and this lack of association persisted after adjustment for potential confounding factors including age, race, sex, education, individual smoking, and method of control selection.

Site specific relative risk estimates were calculated for 13 different sites, even though for many sites the number of cases is too small for detailed analysis. For most sites, the RR in relation to maternal smoking was close to one (Table 2). However, the RR for leukemia and lymphoma was 2.7 (95 per cent confidence limits = 1.3, 5.8). The RR for hematopoietic cancers associated with maternal smoking is greater for individuals whose fathers also smoked (2.6 vs 1.5 for nonsmoking fathers), but the RR remained elevated (RR = 2.4, 95 per cent confidence limits = 1.0, 5.5) after adjusting for father's smoking. Adjustment for age, race, sex, education, and individual smoking did not change this finding. The numbers of specific hematopoietic cancers are small precluding detailed analysis. However, the crude RR for Hodgkins disease (RR = 4.4, 95 per cent confidence limits = 1.1, 4.6), non-Hodgkins lymphomas (RR = 1.7, 95 per cent confidence limits = 0.5, 5.2) and acute leukemias (RR = 8.8, 95 per cent confidence limits = 2.0, 40.0) were greater than one.

TABLE 1—Comparisons of Cases and Controls

Factor	Cases N (%)	Controls N (%)
Total	438 (100)	470 (100)
Age (years)		
<30	83 (19)	89 (19)
30–39	72 (16)	95 (20)
40–49	117 (27)	110 (23)
50–59	166 (38)	176 (37)
Mean Age	43	43
Race		
White	325 (74)	340 (72)
Non-White	113 (26)	130 (28)
Sex		
Male	147 (34)	158 (34)
Female	291 (66)	312 (66)
Education†		
<12 years	182 (42)	164 (35)
12 years	122 (28)	171 (36)
>12 years	133 (30)	135 (29)
Occupation†		
Blue Collar	158 (39)	154 (34)
White Collar	154 (38)	183 (40)
"Housewife"	97 (24)	118 (26)
Smoking Status		
Nonsmoker	197 (45)	223 (47)
Smoker	241 (55)	247 (53)
Mother's Smoking†		
No	353 (84)	389 (85)
Yes	65 (16)	66 (15)
Father's Smoking†		
No	186 (44)	234 (58)
Yes	212 (56)	204 (47)

†Numbers reduced because of missing values.

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TABLE 2—Cancer Risk from Mother's Smoking, All Sites Combined and Selected Sites

Site	Cases		Crude RR	95% Conf. limits
	No.	(% exposed)†		
All Sites	418*	(16)	1.1	(0.7, 1.6)
"Smoking Related"	131	(13)	0.9	(0.5, 1.6)
Not "Smoking Related"	287	(17)	1.2	(0.8, 1.8)
Lip, Oral Cavity and Pharynx	17	(12)	0.8	(0.2, 3.5)
Digestive System	31	(10)	0.6	(0.2, 2.1)
Respiratory System	22	(14)	0.9	(0.3, 3.2)
Lung	15	(13)	0.9	(0.2, 4.1)
Bone, Skin and Connective Tissue	36	(8)	0.5	(0.2, 1.8)
Breast‡	53	(15)	0.9	(0.4, 2.1)
Female Genital Tract‡	133	(17)	1.1	(0.7, 2.2)
Cervix‡	80	(15)	0.9	(0.6, 1.9)
Prostate§	10	(0)	0.0	(0.0, 3.7)¶
Testis§	5	(20)	1.8	(0.2, 16.6)
Urinary Tract	6	(0)	0.0	(0.0, 5.1)¶
Eye, Brain and Other Nervous System	37	(11)	0.7	(0.2, 2.1)
Brain	31	(13)	0.9	(0.3, 2.7)
Endocrine Glands	21	(19)	1.4	(0.5, 4.2)
Hematopoietic Tissue	41	(32)	2.7	(1.3, 5.8)
Other	6	(17)	1.2	(0.1, 10.3)

*Missing values for mother's smoking
†For comparison 86 (15%) of 455 controls were exposed to mother's smoking
‡Sex specific comparison 18% of 301 female controls were exposed
§Sex specific comparison 12% of 154 male controls were exposed
¶Exact confidence limits

Paternal Smoking

There was an overall relative risk estimate of 1.5 (95 per cent confidence limits = 1.1, 2.0) for cancer among individuals whose fathers smoked in the household (Table 3). Adjusting for potential differences in age, sex, race, individual smoking status, smoking by spouse, education, maternal smoking, or method of control selection did not alter this finding (RR = 1.5). Estimates of the adjusted RR were obtained separately for the group with friend controls (RR = 1.6) and the group with population controls (RR = 1.4). The combined adjusted RR in a matched pairs analysis with a much smaller data set was also similar. The RR for cancer associated with father's smoking was greater for males than females (1.7 vs 1.4), for non-Whites than for Whites (1.7 vs 1.4), and for smokers than for nonsmokers (1.7 vs 1.2).

TABLE 3—Cancer Risk from Father's Smoking, All Sites Combined and Selected Sites

Site	Cases		Crude RR	95% Conf. limits
	No.	(% exposed)†		
All Sites	378*	(56)	1.5	(1.1, 2.0)
"Smoking Related"	120	(58)	1.6	(1.0, 2.5)
Not "Smoking Related"	258	(55)	1.4	(1.0, 1.9)
Lip, Oral Cavity and Pharynx	17	(53)	1.3	(0.4, 3.8)
Digestive System	30	(60)	1.7	(0.8, 3.9)
Respiratory System	22	(50)	1.1	(0.5, 2.9)
Lung	13	(62)	1.8	(0.5, 6.6)
Bone, Skin and Connective Tissue	34	(32)	0.5	(0.2, 1.2)
Breast‡	51	(51)	1.1	(0.6, 2.1)
Female Genital Tract‡	113	(60)	1.8	(1.0, 2.6)
Cervix‡	70	(61)	1.7	(1.0, 3.0)
Prostate§	9	(44)	1.0	(0.2, 4.7)
Testis§	5	(80)	5.2	(0.5, 125.9)
Urinary Tract	5	(40)	0.8	(0.1, 5.7)
Eye, Brain and Other Nervous System	30	(63)	2.0	(0.9, 4.6)
Brain	24	(67)	2.3	(0.9, 6.0)
Endocrine Glands	20	(55)	1.4	(0.5, 3.8)
Hematopoietic Tissue	37	(68)	2.4	(1.1, 5.2)
Other	5	(80)	4.6	(0.5, 108.7)

*Missing values for father's smoking
†For comparison 47% of 438 controls were exposed to father's smoking
‡Sex specific comparison 48% of 288 female controls were exposed
§Sex specific comparison 43% of 150 male controls were exposed

Crude estimates of relative risk for cancers at specific sites in relation to father's smoking are shown in Table 3. The RR for "smoking related" (RR = 1.6) and for "not smoking related" sites (RR = 1.4) are similar. Specific sites with elevated RR included cervix, brain, and hematopoietic tissue.

The RR of 1.7 for cervical cancer among individuals whose fathers smoked is unaffected by adjustment for age, race, sex, maternal smoking, individual smoking, or spouse smoking. The two-fold increase in risk for brain tumors in relation to paternal smoking is similarly unaffected by adjustment for potential confounding variables. Although the number of lung cancer cases with data on father's smoking is small (n = 13), the crude RR for lung cancer associated with father's smoking is 1.8, and is 2.5 after adjusting for age and individual smoking. The RR remains elevated when smoking by spouse and mother are also taken into consideration.

Leukemia and lymphoma risk is also not substantially changed by adjustment for age, sex, race, spouse smoking, and individual smoking. The adjusted RR is 2.5. However, the risk is greater for individuals whose mothers also smoked (RR = 3.1 vs 1.8 for individuals whose mothers did not smoke) and the RR is 1.9 (95 per cent confidence limits = 0.9, 4.4) after adjusting for maternal smoking. For specific hematopoietic cancers, the crude RR was elevated for Hodgkins disease (RR = 5.7, 95 per cent confidence limits = 1.2, 38.4), non-Hodgkins lymphomas (RR = 1.6, 95 per cent confidence limits = 0.6, 4.3), and for acute leukemias (RR = 4.6, 95 per cent confidence limits = 0.6, 34.2).

Individual Smoking Status

Overall and site specific relative risk estimates are shown separately for individuals who smoked and those who never smoked in Table 4. Relative risk estimates in relation to mother's smoking are similar for smokers and nonsmokers and are close to one for all sites but hematopoietic tissue. Increased cancer risk related to father's smoking is not limited to smokers or nonsmokers, although the RR for all sites combined is greater among smokers.

Dose-response

The elevated risks for all cancers combined and for most specific sites were related primarily to father's smoking. However, for leukemia and lymphoma there is an increase in risk when both parents smoked. The RR is 1.7 when one parent smoked and 4.6 if both parents smoked (Mantel-Haenszel chi for trend = 3.25, $p < 0.001$). For both mother's and father's smoking, overall cancer risk increased only slightly with reported frequency of smoking in the house. Risk also tended to increase with reported number of cigarettes smoked, but a large proportion of missing values make these data unreliable.

Discussion

We have found overall cancer risk to be increased among the offspring of men who smoked. There was only a

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TABLE 4—Cancer Risk from Parental Smoking among Nonsmokers and Smokers, All Sites Combined and Selected Sites†

Site	Maternal moking						Paternal moking					
	Nonsmokers			Smokers			Nonsmokers			Smokers		
	No	(% exposed)‡	RR	No	(% exposed)‡	RR	No	(% exposed)§	RR	No	(% exposed)§	RR
All Sites	191	(12)	1.2	227	(19)	1.0	173	(49)	1.2	205	(62)	1.7
"Smoking Related"	47	(9)	0.8	84	(15)	0.8	41	(56)	1.7	79	(59)	1.5
Not "Smoking Related"	144	(13)	1.3	143	(20)	1.1	132	(46)	1.1	126	(64)	1.8
Lip, Oral Cavity, and Pharynx	0	—	—	17	(12)	0.6	0	—	—	17	(53)	1.1
Digestive System	13	(8)	0.7	18	(11)	0.6	12	(50)	1.3	18	(67)	1.7
Respiratory System	4	(25)	2.9	18	(11)	0.6	4	(50)	1.3	18	(50)	1.0
Lung	1	(0)	0.0	14	(14)	0.7	1	(100)	∞	12	(58)	1.4
Bone, Skin, and Connective Tissue	19	(11)	1.0	17	(6)	0.3	20	(30)	0.6	14	(36)	0.6
Breast	29	(10)	0.9	24	(21)	0.9	28	(43)	0.9	23	(61)	1.4
Female Genital Tract	72	(11)	1.0	61	(25)	1.2	59	(51)	1.3	54	(70)	2.2
Cervix	40	(8)	0.7	40	(23)	1.3	34	(56)	1.7	36	(67)	2.0
Eye, Brain and Other Nervous System	17	(6)	0.5	20	(15)	0.8	15	(53)	1.5	15	(73)	2.8
Brain	11	(9)	0.9	20	(15)	0.8	9	(56)	1.7	15	(73)	2.8
Endocrine Glands	11	(18)	1.9	10	(20)	1.1	11	(55)	1.6	9	(56)	1.3
Hematopoietic Tissue	19	(21)	2.3	22	(41)	3.1	17	(65)	2.4	20	(70)	2.4

†Sites with 15 or more cases
‡For comparison, 11% of 220 nonsmoking controls and 18% of 235 smoking controls exposed to mother's smoking
§For comparison, 43% of 211 nonsmoking controls and 50% of 227 smoking controls exposed to father's smoking
∥Sex specific comparison: 45% of nonsmoking controls exposed to father's smoking and 11% exposed to mother's smoking; 52% of smoking controls exposed to father's smoking and 22% exposed to mother's smoking

small increase in risk associated with maternal smoking. Increased risk associated with father's smoking did not appear to be explained by differences in such factors as age, race, sex, social class (as measured by education and occupation), or smoking habits of the case or control. The effect was not limited to known smoking related sites. Estimated relative risks associated with father's smoking tended to be greater for smokers, males, and non-Whites. We have previously reported an increased cancer risk for individuals married to smokers,[29] but the apparent effect of paternal smoking is not altered by adjustment for smoking by spouse.

Several findings from different sources support the plausibility of increased cancer risk from early life exposure to cigarette smoke. In addition to the experimental studies[1-9] and biochemical studies in humans,[10-21] limited support for the results of the present study can be found in other epidemiologic studies.[22-24,27] Only one of these studies, however, has reported on cancer risk during adulthood from exposure to parent's cigarette smoke.[27]

Stewart, *et al*, in a large case-control study, found a very small (RR = 1.1) increased risk for cancer in children up to age 10 whose mothers smoked.[34] An increased cancer risk related to father's smoking was not seen (RR = 1.0), but 10 years may have been too soon to detect an effect. Neutel and Buck[22] found an increased risk (RR = 1.3) in a prospective study of cancer risk through age 10 among children whose mothers smoked during pregnancy, but did not report on father's smoking.

Questions on parental smoking during pregnancy have been included in a number of case-control studies of particular childhood tumors. Our finding of a two-fold increase in risk for brain cancer among individuals whose fathers smoked is consistent with the data of Preston-Martin, *et al*.[23] In their study, which focused on exposure to nitrosamines, an increased risk of brain cancer (RR = 1.5) among children whose fathers smoked during the mother's pregnancy was seen. Sidestream cigarette smoke which is passively inhaled is one source of exposure to nitrosamines and other N-nitroso compounds.[28] Gold, *et al*, did not report on father's smoking but found a five-fold increase in risk for brain tumors among children whose mothers continued to smoke in pregnancy.[35]

Findings from a study by Grufferman, *et al*,[24] are consistent with our finding of a predominantly paternal effect. In that study, an elevated relative risk for rhabdomyosarcoma was associated only with father's smoking. Manning and Carroll reported no increased risk for childhood leukemia related to mother's smoking.[25] Father's smoking was not reported. Although the number of cases was small and dose-response data were inconsistent, Neutel and Buck did find that the offspring of smoking women had nearly twice the leukemia risk of offspring of women who did not smoke.[22]

Despite the small number of lung cancer cases included, we chose to look at lung cancer risk in relation to paternal smoking because of continued interest in passive smoking and cancer risk at this site.[27,36,37] The RR for lung cancer among individuals whose fathers smoked was 2.5 after adjusting for age and individual smoking. The adjusted RR associated with mother's smoking was 1.8, but this was based on only two smoking mothers among 15 cases. Correa, *et al*, reported an RR of 1.7 for lung cancer associated with mother's smoking, but no increased risk related to father's smoking.[27]

Our finding of a possible cervical cancer risk related to father's smoking has not been reported elsewhere. There is, however, growing support for a role of passive smoking (as measured by spouse smoking) in cervical cancer risk.[38,39]

Data on parental smoking were obtained retrospectively from offspring who may not be in a position to provide accurate histories. Parents or siblings of study subjects were

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also interviewed regarding the smoking histories of the parents to validate the data obtained from subjects. We interviewed 649 relatives of subjects included in this report. Of these, 55 per cent were mothers and 40 per cent were siblings. For more than 350 subject-mother pairs, agreement on qualitative smoking questions ranged from 93 to 98 per cent and was substantially better than chance. There was also good agreement between subjects and their siblings.

Our findings are not due to any obvious recall bias. The hypothesis that parental smoking may cause cancer is not generally well known and study subjects and interviewers were told only that we were interested in smoking patterns in families. We obtained similar responses from mothers and subjects, regardless of case status, suggesting that differential recall probably did not occur.

It is difficult to distinguish transplacental and passive childhood exposures in an epidemiologic study: women who smoke during pregnancy generally continue smoking after the baby is born.[40] Father's smoking may produce transplacental as well as passive childhood exposure.[13,16,20] An effect of father's smoking on genetic material in sperm is also a possibility.[41–45] Only 16 per cent of the smoking mothers in our study began smoking after pregnancy, and no mothers smoked only during pregnancy. This made it difficult to compare cancer risks for individuals exposed in utero with risk in individuals exposed only passively in childhood. Furthermore, 94 per cent of the smoking fathers smoked both before and after the subject's birth.

Nevertheless, if an increased risk were seen for mother's but not father's smoking, a transplacental effect might be a reasonable explanation. In this study and others,[23,24] increased risks were generally related to father's smoking only. Little increased risk was associated with mother's smoking, suggesting a passive rather than a transplacental mechanism. Our failure to find a similar effect for mother's smoking might be due to the fact that they smoked fewer cigarettes than fathers or smoked different types of cigarettes. Although children may spend more time with their mothers than with their fathers, it is also conceivable that mothers do not smoke when actively engaged in child care activities.

The increasing frequency of women smoking after the 1920s should provide future studies with increasing power to detect any late effects of maternal smoking on offspring. The first sizable cohort of individuals exposed to maternal smoking is only beginning to reach the age at which cancer most commonly occurs.

REFERENCES

1. Everson RB: Individuals transplacentally exposed to maternal smoking may be at increased cancer risk in adult life. Lancet 1980; 2:123–127.
2. Druckrey H, Preussmann R, Ivankovic S: N-nitroso compounds in organotropic and tranplacental carcinogenesis. Ann NY Acad Sci 1969; 163:676–696.
3. Rice JM: Perinatal period and pregnancy: intervals of high risk for chemical carcinogens. Environ Health Perspect 1979; 29:23–27.
4. Vesselinovitch SD, Rao KVN, Mihailovich N: Neoplastic response to mouse tissues during perinatal age periods and its significance in chemical carcinogenesis. *In*: Bailar JC, Weisburger EK, Aaronson SA, *et al* (eds): Perinatal Carcinogenesis. Nat Cancer Inst Monogr 1979; 51:239–250. DHEW Pub. No. (NIH) 79-1633. Washington, DC: Govt Printing Office, 1979.
5. Drew RT, Boorman GA, Haseman JK, McConnell EE, Busey WM, Moore JA: The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Tox Appl Pharmacol 1983; 68:120–130.
6. Wechsler W, Rice JM, Vesselinovitch SD: Transplacental and neonatal induction of neurogenic tumors in mice: comparison with related species and with human pediatric neoplasms. *In*: Bailar JC, Weisburger EK, Aaronson SA, *et al* (eds): Perinatal Carcinogenesis. Nat Cancer Inst Monogr 1979; 51:219–226.
7. Vesselinovitch SD: Comparative studies on perinatal carcinogenesis. *In*: Tomatis L, Mohr U (eds): Transplacental Carcinogenesis. IARC Sci Pub. No. 4. Lyon: IARC, 1973, 14–22.
8. Napalkov NP: Some general considerations on the problem of transplacental carcinogenesis. *In*: Tomatis L, Mohr U (eds): Transplacental Carcinogenesis. IARC Sci Pub. No. 4. Lyon: IARC, 1973, 1–13.
9. Rice JM: An overview of transplacental chemical carcinogenesis. Teratology 1973; 8:113–126.
10. Lucier GW, Lui EMK, Lamartiniere CA: Metabolic activation/deactivation reactions during perinatal development. Environ Health Perspect 1979; 29:7–16.
11. Jones AH, Fantel AG, Kocan RA, Juchau MR: Bioactivation of procarcinogens to mutagens in human fetal and placental tissues. Life Sci 1977; 21:1831–1836.
12. Rifkind AB, Tseng L, Hirsch MB, Lauersen NH: Aryl hydrocarbon hydroxylase activity and microsomal cytochrome content of human fetal tissues. Cancer Res 1978; 38:1572–1577.
13. Smith N, Austen J, Rolles CJ: Tertiary smoking by the fetus (letter). Lancet 1982; 1:1252.
14. Andrews J: Thiocyanate and smoking in pregnancy. Br J Obstet Gynaecol 1973; 80:810–814.
15. Pettigrew AT, Logan RW, Willocks J: Smoking in pregnancy—effects on birthweight and on cyanide and thiocyanate levels in mother and baby. Br J Obstet Gynaecol 1977; 84:31–34.
16. Bottoms SF, Kuhnert BR, Kuhnert PM, Reese AL: Maternal passive smoking and fetal serum thiocyanate levels. Am J Obstet Gynecol 1982; 144:787–791.
17. Welch RM, Harrison YE, Conney AH, Poppers PJ, Finster M: Cigarette smoking: stimulatory effect on metabolism of 3, 4-benzpyrene by enzymes in human placenta. Science 1968; 160:541–542.
18. Nebert DW, Winker J, Gelboin HV: Aryl hydrocarbon hydroxylase activity in human placenta from cigarette smoking and nonsmoking women. Cancer Res 1969; 29:1763–1769.
19. Vaught JB, Gurtoo HL, Parker NB, LeBoeuf R, Doctor G: Effects of smoking on benzo(a)pyrene metabolism by human placental microsomes. Cancer Res 1979; 39:3177–3183.
20. Manchester DK, Jacoby EH: Sensitivity of human placental monooxygenase activity to maternal smoking. Clin Pharmacol Ther 1981; 30:687–692.
21. Bos RP, Theuws JLG, Henderson PT: Excretion of mutagens in human urine after passive smoking. Cancer Letters 1983; 19:85–90.
22. Neutel CI, Buck C: Effect of smoking during pregnancy on the risk of cancer in children. JNCI 1971; 47:59–63.
23. Preston-Martin S, Yu MC, Benton B, Henderson BE: N-nitroso compounds and childhood brain tumors. A case-control study. Cancer Res 1982; 42:5240–5245.
24. Grufferman S, Wang HH, DeLong ER, Kimm SYS, Delzell ES, Falletta JM: Environmental factors in the etiology of rhabdomyosarcoma in childhood. JNCI 1982; 68:107–113.
25. Manning MD, Carroll BE: Some epidemiological aspects of leukemia in children. JNCI 1957; 19:1087–1094.
26. Jaffe N, Marchetto DJ, Meadows A, Winston KR, Li FP, Scher CD: Clinical investigations of the etiology of childhood cancers. Proc Am Assoc Cancer Res 1978; 19:157.
27. Correa P, Pickle LW, Fontham E, *et al*: Passive smoking and lung cancer. Lancet 1983; 2:595–597.
28. US Department of Health and Human Services: The health consequences of smoking—cancer: a report of the Surgeon General. DHHS Pub. No. (PHS) 82-50179. Washington, DC: Govt Printing Office, 1982.
29. Sandler DP, Everson RB, Wilcox AJ: Passive smoking in adulthood and cancer risk. Am J Epidemiol 185; 121:37–48.
30. Haenszel W, Shimkin MB, Miller HP: Tobacco smoking patterns in the United States. Public Health Monogr No. 45.1956:56.
31. Harris JE: Cigarette smoking among successive birth cohorts of men and women in the United States during 1900–80. JNCI 1983; 71:473–479.
32. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies. JNCI 1959; 22:719–748.
33. Gart JJ: Point and interval estimation of the common odds ratio in the combination of 2 × 2 tables with fixed marginals. Biometrika 1970; 57:471–475.
34. Stewart A, Webb J, Hewitt D: A survey of childhood malignancies. Br Med J 1958; 1:1495–1508.
35. Gold E, Gordis L, Tonascia J, Szklo M: Risk factors for brain tumors in children. Am J Epidemiol 1979; 109:309–319.
36. Hirayama T: Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 1981; 282:183–185.
37. Trichopoulos D, Kalandidi A, Sparros L, *et al*: Lung cancer and passive smoking. Int J Cancer 1981; 27:1–4.

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38. Buckley JD, Harris RWC, Doll R, *et al.* Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981; 2:1010–1015.
39. Brown DC, Pereira L, Garner JB. Cancer of the cervix and the smoking husband. Can Fam Physician 1982; 28:499–502.
40. McMahon B, Alpert M, Salber EJ. Maternal weight and prenatal smoking habits. Am J Epidemiol 1966; 82:247–261.
41. Tomatis L, Cabral JRP, Likhachev AJ, Ponomarkov V: Increased cancer incidence in the progeny of male rats exposed to ethylnitrosourea before mating. Int J Cancer 1981; 28:475–478.
42. Nomura T: Parental exposure to X-rays and chemicals induces heritable tumours and anomalies in mice. Nature 1982; 296:575–577.
43. Evans HJ: Parental mutagenesis and familial cancer. Nature 1982; 296:488–489.
44. Evans HJ, Fletcher J, Torrance J, Hargreave TB: Sperm abnormalities and cigarette smoking. Lancet 1981; 1:627–629.
45. Grufferman S, Delzell ES, Maile MC, Michaelopoulos G: Parents' cigarette smoking and childhood cancer. Med Hypoth 1983; 12:17–20.

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Mortality Rates in Boston (and Other Large Cities), 1911

Boston's death rate for 1911 was 17.1, which is high compared with rates of most other large American cities.

The 1911 rates for the other cities having over 500,000 inhabitants were—Cleveland 13.55; Pittsburgh 14.94; Chicago 14.55; New York 15.22; St. Louis 15.36; Philadelphia 16.51; and Baltimore 18.43.

A brief analysis of these rates is desirable.

Typhoid Fever:—*From typhoid Boston had the lowest rate of all the cities. The rates per 100,000 were as follows:—Boston 9.14; Chicago 10.78; New York 10.99; Philadelphia 14.11; Cleveland 14.46; St. Louis 15.56; Pittsburgh 25.81; and Baltimore 27.28.*

Scarlet Fever:—*The rates were Baltimore 7.79; Pittsburgh 9.95; Boston 10.74; Philadelphia 11.33; New York 13.25; Chicago 21.20; St. Louis 27.26; and Cleveland 31.12.*

Diphtheria:—*The rates were Baltimore 12.05; St. Louis 16.84; Boston 18.00; Cleveland 21.94; Pittsburgh 23.60; New York 25.84; Philadelphia 31.51; and Chicago 39.11.*

Measles:—*The rates were Chicago 5.75; Cleveland 6.63; Pittsburgh 9.59; Boston 10.74; New York 13.25; Baltimore 13.63; St. Louis 15.84; and Philadelphia 19.30.*

Whooping Cough:—*The rates were Chicago 2.45; St. Louis 4.57; Philadelphia 7.34; New York 7.75; Baltimore 8.50; Cleveland 14.80; Boston 15.68; and Pittsburgh 19.54.*

Taking all these diseases together, Boston had the lowest rate with 64.30 per 100,000; the others in order were Baltimore 69.25; New York 70.88; Chicago 7.29; St. Louis 80.07; Philadelphia 83.59; Pittsburgh 88.49; and Cleveland 88.95.

Tuberculosis of the Lungs:—*The rates per 100,000 were Cleveland 121.77; Pittsburgh 130.88; St. Louis 135.29; Boston 154.88; Chicago 165.98; New York 177.39; Philadelphia 187.31; and Baltimore 205.12.*

This analysis of the communicable diseases should be extremely gratifying to the people of Boston. However, it fails to reveal the reason of Boston's higher rate. But a study of the figures for 1910, for which year more complete figures are available, will show much more. . . .

Cancer, cerebral hemorrhage, organic diseases of the heart, pneumonia and violent deaths stand out as the principal causes which have comparatively high rates in Boston. . . .

There are two reasons why Boston has such a large number of deaths of non-residents. First it has a population in its immediate suburbs greater than the population of the city itself. These people labor in Boston and when ill come to Boston hospitals. The other reason is that Boston is the recognized medical centre for all New England and attracts those afflicted with cancer, for example, a disease more prevalent in the New England States than in any of the other registration states.

Moreover in 1910 Boston had a larger percentage of its deaths over 6 years of age than any of the cities under consideration. In a word, Boston is an old city and has many old people. . . .

But in a word it may be safely said that Boston's high rate is largely due to its geographical position in the centre of populous suburbs, and to its fame as a medical centre, and not, as has been so often intimated, to the unhealthful conditions in the city.

—Davis WH: Boston's death rate. Am J Public Health 1912; 2:638–640.

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Letters to the Editor

BREAST CANCER, CIGARETTE SMOKING, AND PASSIVE SMOKING

In recent papers on cigarette smoking and breast cancer (1–6), as in all earlier such papers, the reference category was women who had never smoked. Yet there is evidence, some published, some unpublished, that passive smoking among never smokers could increase breast cancer risk. Thus, a better reference category for these studies may be women who never smoked and who have no reported exposure to environmental tobacco smoke.

Hirayama (7) has mentioned breast cancer as possibly associated with passive smoking. For this communication, Dr. Hirayama (personal communication, 1988) has provided detailed mortality data (table 1) for never smoking women according to husband's smoking habit. The data show an elevated risk of breast cancer in never smokers whose husbands smoked. Sandler et al. (8–10) report an association between passive smoking and breast cancer. Data provided by Dr. Sandler (personal communication, 1986) also show an increased risk of breast cancer in never smoking women whose husbands smoked (table 2). Miller (11) also reported an association of passive smoking with breast cancer. Horton (12) correlated male lung cancer incidence with female breast cancer incidence in various countries and various parts of the United States, also suggesting that ambient tobacco smoke may be related to breast cancer.

A reasonable estimate for the relative risk of passive smoking breast cancer based on both the Hirayama and Sandler data sets would be about 1.4 for all ages combined. For women under 50 years of age, considering the known lag time between incidence and death, the best estimate for relative risk is about two. The fraction of never smoking women exposed passively to smoke can be estimated as follows. The fraction of controls living with smokers in all 14 US passive smoking studies through 1987 (13) is 60 percent. Friedman et al. (14) indicate that, additionally, 40 percent of nonsmoking women married to nonsmoking husbands are exposed to ambient tobacco smoke. Thus the total percent exposed would be 60% + 0.40 × 40% = 76%. The estimated relative risk of breast cancer for all never smokers compared with nonexposed never smokers would then be 1.3 (1.4 × 0.76 + 1.0 × 0.24), and the incidence risk for those under age 50 would be about 1.8 (2 × 0.76 + 1.0 × 0.24).

If we consider as an example the study by Rohan and Baron (1) of breast cancer and active smoking, we can show the effect of a passive smoking adjustment on their data for current smokers (all ages) (table 3). The odds ratio for breast cancer in active smokers is raised from a nonsignificant 1.3 to a statistically significant 1.7. The premenopausal odds ratio for breast cancer for currently smoking women in Rohan and Baron's table 3 would likewise be adjusted upward from 1.32 to 2.4 (1.32 × 1.8).

The results in the various papers on active smoking and breast cancer are at best confusing. However, adjusting for a presumed association of passive smoking with breast cancer would elevate probably all of the smoking relative risks to a level greater than unity. Averaging the rather scattered results for the six studies cited (1–6) yields excess risks for current smokers that are about twice those for passive smokers and ex-smokers. Such a result is consistent with one of the explanations proposed by Rohan and Baron, namely that the results reflect an unstable balance between direct (carcinogenic) and indirect (hormonal) effects, but with the added thought that the protective hormonal effects are greater at the higher levels of exposure. An additional possibility is that most of the breast carcinogenic damage may be coming from vapor phase constituents in the cigarette smoke. Recent evidence (15) indicates that 70 percent of the tar in environmental tobacco smoke is in the vapor phase, whereas all of the tar in direct smoking is in the particulate phase. Particulate phase smoke tends to be cleared into the mouth and swallowed, while vapor phase constituents absorb into the blood and lymph systems. This may mean that, unlike lung cancer, breast cancer effects from direct smoking may be coming primarily from the va-

TABLE 1. Relative n
husband, in a prospe

Husband's age at enrollment (years)	
40–49	
Cases	
Population	
50–59	
Cases	
Population	
60–69	
Cases	
Population	
70–79	
Cases	
Population	
Total, all ages	
Cases	
Population	

* Case and populati

TABLE 2. Relative ris
husband, in a case-co

Wife's a interview	
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TABLE 3. The effect o
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TABLE 1. Relative risk of mortality for breast cancer in never smoking women, by age group and smoking habit of the husband, in a prospective study in Japan, 1966–1981*

Husband's age at enrollment (years)	Husband's smoking habit (no. of cigarettes per day)						Relative risk, husband an ever smoker	95% confidence interval
	Ex-smoker	1–14	15–19	20+	Ever smoker	Never smoker		
40–49								
Cases	1	12	4	7	24	4	1.5	0.5–4.2
Population	1,255	8,621	5,158	10,764	25,798	6,229		
50–59								
Cases	5	15	3	20	43	8	1.6	0.8–3.5
Population	1,922	9,668	4,052	9,820	25,462	7,791		
60–69								
Cases	2	8	2	10	22	9	1.0	0.5–2.1
Population	2,687	7,243	2,513	4,651	17,094	7,120		
70–79								
Cases	1	0	0	2	3	2	0.9	0.2–5.2
Population	348	612	105	226	1,291	755	—	—
Total, all ages								
Cases	9	35	9	39	92	23	1.26	0.8–2.0
Population	6,212	26,144	11,828	25,461	69,645	21,895		

* Case and population data are from a personal communication from Dr. Hirayama.

TABLE 2. Relative risk of breast cancer in never smoking women, by age and menopausal status and by smoking habit of husband, in a case-control study in North Carolina, 1979–1981*

Wife's age at interview (years)	Husband's smoking habit		Odds ratio	95% confidence interval
	Ever	Never		
<40				
Cases	4	2	4.4	0.9–23.1
Controls	24	53		
40–49				
Cases	9	4	2.9	0.7–11.0
Controls	15	19		
50–59				
Cases	6	4	1.1	0.3–4.5
Controls	27	20		
60+				
Cases	0	3	0.0	
Controls	10	9	—	—
Totals, all ages				
Cases	19	13	1.94	0.9–4.2
Controls	76	101		
Premenopausal				
Cases	6	2	7.1	1.6–31.3
Controls	27	64		
Postmenopausal				
Cases	13	11	0.9	0.4–2.2
Controls	49	37		

* Case and control data from a personal communication from Dr. Sandler.

TABLE 3. The effect of adjustment for passive smoking on current smoking risk for breast cancer in table 2 of Rohan and Baron (1)

	Smoking status		Never smoked, based on 76% passively exposed	
	Current smoker	Never smoked	Exposed	Not exposed
Cases	108	254	201	53
Controls	88	273	199	74
Total	196	527	400	127
Crude odds ratio vs. never smoked	1.32	1.00	1.09	0.77
95% confidence interval	0.95–1.83		0.84–1.41	0.52–1.14
Crude odds ratio vs. nonexposed never smoked	1.71	1.30	1.41	1.00
95% confidence interval	1.09–2.69	0.88–1.92	0.94–2.11	

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por phase smoke, in other words, more from the smoker's passive smoking than from the smoke directly inhaled from the cigarette.

The intent of this letter is not to "prove" an association between breast cancer and passive or direct smoking. Rather, it is to alert researchers in the breast cancer field to consider seriously, as a reference category in future studies, the use of never smokers who have had little or no exposure to environmental tobacco smoke. Considering the long induction periods involved in breast cancer, it will be necessary to trace histories of passive exposure over long periods of time in order to get meaningful data. Only by performing such investigations can we determine the real risk, if any, of breast cancer from various degrees of passive smoking and thus determine the real risk, if any, from direct smoking.

REFERENCES

1. Rohan TE, Baron JA. Cigarette smoking and breast cancer. Am J Epidemiol 1989;129:36–42.
2. Rosenberg L, Schwingl PJ, Kaufman DW, et al. Breast cancer and cigarette smoking. N Engl J Med 1984;310:92–4.
3. Brinton LA, Schairer C, Stanford JL, et al. Cigarette smoking and breast cancer. Am J Epidemiol 1986;123:614–22.
4. Brownson RC, Blackwell CW, Pearson DK, et al. Cigarette smoking and breast cancer in relation to cigarette smoking. Arch Intern Med 1988;148:140–4.
5. Schechter MT, Miller AB, Howe GR. Cigarette smoking and breast cancer: a case-control study of screening program participants. Am J Epidemiol 1985;121:479–87.
6. Schechter MT, Miller AB, Howe GR, et al. Cigarette smoking and breast cancer: case-control studies of prevalent and incident cancer in the Canadian National Breast Screening Study. Am J Epidemiol 1989;130:213–20.
7. Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev Med 1984;13:680–90.
8. Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. Am J Epidemiol 1985;121:37–48.
9. Sandler DP, Wilcox AJ, Everson RB. Cumulative effects of lifetime passive smoking on cancer risk. Lancet 1985;1:312–15.
10. Sandler DP, Everson RB, Wilcox AJ. Cigarette smoking and breast cancer. (Letter.) Am J Epidemiol 1986;123:370–1.
11. Miller GH. The impact of passive smoking: cancer deaths among nonsmoking women. Paper presented at the 7th International Symposium on Prevention and Detection of Cancer, Nice, France, April 13–15, 1989.
12. Horton AW. Indoor tobacco smoke pollution: a major risk factor for both breast and lung cancer? Cancer 1988;62:6–14.
13. Wells AJ. An estimate of adult mortality in the United States from passive smoking. Environ Int 1988;14:249–65.
14. Friedman GD, Petitti DB, Bawol RD. Prevalence and correlates of passive smoking. Am J Public Health 1983;73:401–5.
15. Pritchard JN, Black A, McAughey JJ. The physical behavior of sidestream tobacco smoke under ambient conditions. Environ Technol Lett 1988; 9:545–52.

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✓ *COMMENT BY DR. SANDLER*

While many will not be convinced of the biologic plausibility of a breast cancer risk from passive smoking, the example provided by Wells (1) illustrates the potential hazard of dismissing, a priori, the possibility of such an effect. His argument holds for other conditions which may later be found to be smoking-related, and points to the need for identifying truly unexposed comparison groups in epidemiologic studies.

REFERENCE

1. Wells AJ. Breast cancer, cigarette smoking, and passive smoking. (Letter.) Am J Epidemiol 1991;133:208–10.

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RE: "WARTIME DETERMINANTS OF ARTERIOGRAPHICALLY CONFIRMED CORONARY ARTERY DISEASE IN BEIRUT"

Sibai et al. (1) have reported associations between exposure to both acute and chronic war events and artiographically confirmed coronary artery disease. They indicate that the significant associations were consistent using both the arteriography series approach of separating cases from "patient co
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Bladder Cancer in Nonsmokers

GEOFFREY C. KABAT, PHD, GRETCHEN S. DIECK, PHD, AND ERNST L. WYNDER, MD

Potential risk factors for bladder cancer were studied in a series of 76 male and 76 female bladder cancer cases and 238 male and 254 female controls who reported never having smoked. Risk factors included usual occupation, smoking by the spouse, sidestream smoke exposure at home and at work and in transportation, coffee drinking (caffeinated and decaffeinated), artificial sweetener use, body mass index, and a history of diabetes and high blood pressure. No association was found with spouse's smoking or reported sidestream smoke exposure, coffee drinking, artificial sweetener use, or a number of other variables; however, there was some indication that several occupations were overrepresented in the cases. A positive association was found with snuff use in women, but the numbers were small (three cases and one control). Restriction of the study to lifetime nonsmokers permitted the assessment of potential risk factors in the absence of potential confounding and interactive effects of smoking. The study had adequate statistical power to detect moderately small elevated risks due to the main factors examined.

Cancer 57:362-367, 1986.

CIGARETTE SMOKING is a well-established risk factor for bladder cancer, as is occupational exposure to specific carcinogens[1-3]; however, it is generally agreed that a substantial proportion of bladder cancer incidence remains unexplained.[4-6]

In the current study, a number of potential risk factors for bladder cancer are examined in a group of bladder cancer cases and controls who reported never having smoked on a regular basis (*e.g.*, as much as one cigarette, cigar, or pipe per day for 1 year). The restriction of the study to lifetime nonsmokers permits the assessment of potential risk factors in the absence of smoking, which could act as a confounding variable.

Methods

The data used in this analysis derive from a large, ongoing case-control study of smoking and cancer that has been in progress since 1969, as previously described.[7] In this large study, cases consisted of patients with tobacco-related cancers who were interviewed in 18 hospitals in six U. S. cities. Controls were hospitalized patients with current diagnoses of non-tobacco-related diseases and were interviewed in the same hospitals during the same time period, thus providing a pool of controls.

In the current study, all bladder cancer cases interviewed between 1976 and 1983 were selected from the large data base. There was a total of 751 male and 197 female bladder cancer cases during this period. Seventy-six male and 76 female bladder cancer cases reported never having smoked regularly. For each of these never-smoking cases, three controls were sought in the large pool of hospitalized controls. The controls were matched on age (within 5 years), sex, race, hospital, year of interview, and lifetime nonsmoking status. In all, 238 male and 254 female controls were selected (3 controls were not obtained for all cases).

The distribution of diagnoses among the controls was as follows: men, 67.1% non-tobacco-related cancers, 32.9% noncancer diagnoses; women, 59.3% non-tobacco-related cancers, 40.7% noncancer.

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TABLE 1. Distribution of Nonsmoking Bladder Cancer Cases and Controls by Selected Demographic Variables

	M				F			
	Cases		Controls		Cases		Controls	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age								
≤49	15	(19.7)	50	(21.0)	5	(6.6)	20	(7.9)
50–59	20	(26.3)	55	(23.1)	9	(11.8)	30	(11.8)
60–69	30	(39.5)	104	(43.7)	32	(42.1)	116	(45.7)
70+	11	(14.5)	29	(12.2)	30	(39.5)	88	(34.6)
Total	76		238		76		254	
Religion								
Protestant	20	(26.3)	63	(26.5)	29	(38.2)	70	(27.6)
Catholic	29	(38.2)	94	(39.5)	34	(44.7)	125	(49.2)
Jewish	21	(27.6)	60	(25.2)	7	(9.2)	40	(15.7)
Other	6	(7.9)	21	(8.8)	6	(7.9)	19	(7.5)
Total	76		238		76		254	
Years of education*								
1–11	14	(18.7)	47	(20.0)	40	(54.1)	104	(41.4)
12	16	(21.3)	54	(23.0)	16	(21.6)	87	(34.7)
13–15	11	(14.7)	41	(17.4)	8	(10.8)	29	(11.6)
16+	34	(45.3)	93	(39.6)	10	(13.5)	31	(12.3)
Total	75		235		74		251	
Occupational status								
Professional	39	(51.3)	117	(49.2)	11	(14.5)	37	(14.5)
Skilled	22	(29.0)	82	(34.4)	17	(22.4)	86	(33.9)
Semiskilled	9	(11.8)	23	(9.7)	5	(6.6)	16	(6.3)
Unskilled	6	(7.9)	16	(6.7)	8	(10.5)	26	(10.2)
Housewife	—	—	—	—	35	(46.0)	89	(35.0)
Total	76		238		76		254	

* Years of education unknown for one male case, two female cases, three male controls, and three female controls.

All subjects were interviewed in the hospital with a structured questionnaire, which contained questions on demographic factors, residence, usual occupation, self-reported occupational exposures, tobacco smoking, spouse's smoking, exposure to sidestream tobacco smoke, alcohol use, coffee drinking, saccharin use, height, current weight, weight 5 years before current hospitalization, and history of previous diseases.

Usual occupation was assessed by asking each subject what job he had held for the longest period of time. Self-reported occupation was coded according to an abbreviated list of the U. S. Bureau of Census codes.[8] Information on exposure at work or at home to a variety of occupational and environmental substances was elicited from each subject. An individual was classified as exposed to a specific substance if that exposure occurred for at least 8 hours/week for at least 1 year. The number of years of each self-reported exposure was also obtained. Residence at three periods (childhood, adolescence, adulthood) was categorized as urban, rural, or mixed urban and rural. The county and state of longest residence in adulthood was also obtained from those interviewed from 1979 onward.

Information on spouse's smoking status was asked of those individuals who had ever been married. Because questions on passive smoking were added to the questionnaire in 1979, spouse's smoking status was available for only 58% of the nonsmoking bladder cancer cases and controls. Information on exposure to sidestream smoke at home and at work was available for only 21% of the cases and controls.

Usual intake of regular and decaffeinated coffee was determined by asking for the number of cups of each kind drunk per day.

Artificial sweetener use was elicited in terms of whether the subject had ever used either saccharin or cyclamate, as well as number of packets, tablets, or drops consumed per day of saccharin food additives; number of cans consumed per day of artificially sweetened beverages; and years of artificial sweetener use.

Body mass index (BMI) (weight/height^2 × 10,000) was calculated for each subject with the reported weight of 5 years before diagnosis.

History of diabetes mellitus and of high blood pressure was also obtained from each subject.

The measure of association used to examine the rela-

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TABLE 2. Selected Occupations of Male Nonsmoking Bladder Cancer Cases and Controls

Usual occupation	Cases No.	Cases (%)*	Controls No.	Controls (%)†	Odds ratio
Auto mechanics	0	(0.0)	5	(2.1)	0.3
Chemical workers	4	(5.3)	2	(0.8)	6.6‡
Construction workers	0	(0.0)	7	(2.9)	0.2
Electrical workers	2	(2.6)	6	(2.5)	1.1
Farmers	3	(3.9)	1	(0.4)	9.7‡
Firemen	3	(3.9)	0	(0.0)	22.7‡
Machinists	4	(5.3)	3	(1.3)	4.4‡
Physicians	6	(7.9)	2	(0.8)	10.1‡
Policemen	0	(0.0)	5	(2.1)	0.3
Printers	2	(2.6)	6	(2.5)	1.1
Textile workers	0	(0.0)	3	(1.3)	0.4
Truck, bus, taxi drivers	3	(3.9)	8	(3.4)	1.2
Woodworkers	2	(2.6)	1	(0.4)	6.4

* Based on 76 cases.
† Based on 238 controls.
‡ Statistically significant at $P = 0.05$ level.

tionship between variables of interest and bladder cancer is the odds ratio.[9] Corresponding test-based 95% confidence intervals were calculated according to Miettinen.[10]

Results

Information on cell type was available for all nonsmoking bladder cancer cases. The distribution of cell types among the cancer cases was as follows: men, 93.4% transitional cell carcinoma, 3.9% adenocarcinoma, 2.6% squamous cell carcinoma; women, 82.7% transitional cell carcinoma, 6.7% adenocarcinoma, 6.7% squamous cell carcinoma, 2.6% anaplastic, 1.3% papillary and mucinous adenocarcinoma.

The age distributions of the bladder cancer cases and controls are presented in Table 1. Few differences were found between cases and controls with respect to age, because the controls were roughly matched to cases on this variable. Female cases and controls were older, in general, than male cases and controls; mean age of female cases was 66.4 years, compared with 58.9 years for male cases.

Cases and controls differed little by religious affiliation, years of education, or occupational status as derived from self-reported occupational title (Table 1). The large number of subjects classified as professional or managerial reflects the relatively high socioeconomic level of male patients from Memorial Sloan-Kettering, the hospital contributing the most patients to the study population (61% of the men and 45% of the women were from Memorial).

Table 2 presents the frequency distributions of male cases and controls by selected occupations. Although the numbers are extremely small, significantly increased odds ratios for bladder cancer were found among those classified as chemical workers (primarily chemists and chemical engineers), firemen, machinists, and physicians. The increased risk found in physicians is most likely due to selective referral of physicians with bladder cancer seeking treatment at Memorial Sloan-Kettering (only one of the six physician cases was not treated at Memorial).

Among those individuals who had ever been married, bladder cancer cases and controls differed little with respect to whether or not their spouse smoked. Fifteen of the 49 male cases (30.6%) had a wife who had smoked, compared to 50 of the 137 male controls (36.5%). Among women, 24 of the 35 cases (68.6%) had a husband who had smoked compared with 83 of the 129 controls (64.8%). Male cases were somewhat more likely than controls to report exposure to sidestream smoke at home, whereas female cases were less likely to report home exposure (Table 3). These differences were small and did not reach statistical significance. When exposure to sidestream smoke at work or in transportation was examined (Table 4), male cases reported less exposure, whereas female cases reported more exposure than their corre-

TABLE 3. Number of Hours Per Week of Exposure to Sidestream Tobacco Smoke at Home* in Nonsmoking Bladder Cancer Cases and Controls

Hours/week	M Cases No.	M Cases (%)	M Controls No.	M Controls (%)	F Cases No.	F Cases (%)	F Controls No.	F Controls (%)
None	16	(69.6)	34	(77.3)	11	(64.7)	15	(53.6)
<1	1	(4.4)	0	(0)	1	(5.9)	0	(0)
1–2	0	(0)	1	(2.3)	0	(0)	0	(0)
3–4	2	(8.7)	0	(0)	0	(0)	0	(0)
5–9	4	(17.4)	8	(18.2)	1	(5.9)	1	(3.6)
10+	0	(0)	1	(2.3)	4	(23.5)	12	(42.9)
	23		44		17		28	

* This information is available only for those subjects interviewed from 1979 to 1981. The ratio of cases to controls in this table is closer to 1:2 (rather than the 1:3 ratio in other tables) due to the fact that the questionnaire containing this item was given only to a limited number of controls, whereas the remaining items were asked of the entire pool of controls.

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TABLE 4. Number of Hours Per Week of Exposure to Sidestream Tobacco Smoke at Work and in Transportation* in Nonsmoking Bladder Cancer Cases and Controls

	M				F			
	Cases		Controls		Cases		Controls	
Hours/week	No.	(%)	No.	(%)	No.	(%)	No.	(%)
None	12	(52.2)	18	(40.9)	11	(64.7)	23	(82.1)
<1	0	(0)	1	(2.3)	0	(0)	0	(0)
1–2	0	(0)	1	(2.3)	0	(0)	0	(0)
3–4	1	(4.4)	3	(6.8)	0	(0)	1	(3.6)
5–9	4	(17.4)	4	(9.1)	1	(5.9)	0	(0)
10+	6	(26.1)	16	(36.4)	5	(29.4)	4	(14.3)
Don't know	0	(0)	1	(2.3)	0	(0)	0	(0)
	23		44		17		28	

* This information is available only for those subjects interviewed from 1979 to 1981. The ratio of cases to controls in this table is closer to 1:2 (rather than the 1:3 ratio in other tables) due to the fact that the questionnaire containing this item was given only to a limited number of controls, whereas the remaining items were asked of the entire pool of controls.

sponding controls. Again, these differences were not statistically significant.

The distribution of cases and controls by the number of cups of brewed coffee consumed per day are presented in Table 5. None of the odds ratios for drinkers of varying numbers of cups per day was significantly elevated, and there was no suggestion of a trend in either sex. Daily consumption of decaffeinated coffee also showed no association with bladder cancer (Table 6). Cases and controls were similar with respect to daily intake of tea and instant coffee (data not shown).

Among the men, 77.6% of the cases and 80.2% of the controls never used artificial sweeteners, whereas 76.3% of the cases and 79.4% of the controls never drank diet soda. Among the women, the cases were slightly less likely than the controls to use artificial sweeteners or diet drinks (79.0% of the cases, *versus* 76.0% of the controls never used artificial sweeteners, and 84.2% of the cases, compared with 77.2% of the controls, never drank diet soda).

No association with bladder cancer risk was found for BMI, or a history of diabetes or of high blood pressure.

Only one female case and one male case chewed tobacco, and no male cases reported ever having used snuff. Snuff use among women, however, was positively associated with bladder cancer; three cases, compared with one control, had ever used snuff (Fisher's Exact Test, $P = 0.04$). Of the four female snuff users, one case was a current user, and the remaining two cases and one control were exusers. Two cases use or had used snuff constantly; the remaining case used snuff more than 10 times/week, whereas the one control used snuff less than once a week. The three cases used snuff for 1, 31, and 48 years, respectively, whereas the control used snuff for 3 years.

Other variables examined and found not to be associated with bladder cancer included: marital status; place of birth (foreign- or U. S.-born); residence in childhood, adolescence, or adulthood with respect to urban or rural environment; county of longest residence in adulthood; self-reported exposure to a variety of substances; and consumption of wine, beer, and hard liquor.

Discussion

The examination of a variety of possible risk factors for bladder cancer in a homogeneous group of lifetime nonsmokers provided a means of eliminating the potential confounding and interactive effects of smoking, already

TABLE 5. Usual Intake of Brewed Coffee Among Nonsmoking Bladder Cancer Cases and Controls

	M				F			
No. of cups/day	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
None/occasional	40	129	1.00*	—	40	146	1.00*	—
1–2	18	64	0.91	0.48–1.71	24	58	1.51	0.84–2.72
3–4	15	35	1.38	0.69–2.79	8	36	0.81	0.35–1.88
5–6	3	7	1.38	0.34–5.59	2	11	0.66	0.14–3.10
7+	0	3	0.46	0.03–8.47	2	3	2.43	0.41–14.34
	76	238			76	254		

* Referent group.

OR: odds ratio; CI: confidence interval.

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TABLE 6. Current Usual Intake of Decaffeinated Coffee Among Nonsmoking Bladder Cancer Cases and Controls

	M				F			
No. of cups/day	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
None/occasional	60	179	1.00*	—	62	180	1.00*	—
1–2	14	39	1.07	0.54–2.11	9	52	0.50	0.24–1.07
3–4	2	15	0.40	0.09–1.71	5	20	0.73	0.26–2.01
5+	0	5	0.27	0.02–4.10	0	2	0.58	0.03–11.82
	76	238			76	254		

* Referent group.

OR: odds ratio; CI: confidence interval.

established as a major risk factor for the disease. The relatively small number of nonsmoking male and female bladder cancer cases resulted in small numbers when studying subgroups; however, the study had sufficient power to detect moderately small associations. For a variable for which information was available on all study participants, such as decaffeinated coffee use, with an exposure rate in the controls of 30% and an alpha value of 0.05, the power to detect an odds ratio of 1.67 was 90%. For a variable with information missing for some study subjects, such as spouse's smoking in men, the power to detect an odds ratio of 1.5, given an exposure rate in the controls of 36.5% and an alpha of 0.05, was 58%. For spouse's smoking in women with an exposure rate of 65% in the controls, the power to detect an odds ratio of 1.3 was 67%.

The role of occupation in the etiology of bladder cancer has been extensively studied,[11–16] and it has been estimated that as much as 30% of bladder cancer cases may have an occupationally related cause.[17] Elevated risks among chemical workers, machinists, and farmers have been found in some previous studies,[6,12,14,15,18–20] whereas others have not confirmed these findings.[12,13,15,16] Whether the observed elevated risk of bladder cancer in firefighters is due to a common exposure such as smoke inhalation requires further study. There was some suggestion of an increased risk in firemen in a mortality study in Washington State,[16] although the numbers were small. By considering only nonsmokers, the current analysis precludes the chance of showing an interaction between smoking, occupation, and bladder cancer, a possibility suggested by Vineis and colleagues.[21]

The findings of the current study with respect to occupation are limited for several reasons. First, because of the composition of our hospital population (largely middle-class and professional), blue collar industrial occupations are underrepresented. Furthermore, the number of subjects in any one occupational group was small. An additional consideration is that because of the many comparisons made, some may be due to chance alone; however, it is unlikely that all of these findings resulted from chance. As mentioned previously, the association found with physicians is most likely due to referral bias. The physicians did not share a common specialty and have been examined previously and not shown to have an excess risk of bladder cancer.[16] No associations were found between occupation and bladder cancer among the women.

Passive inhalation has recently become a subject of considerable interest, particularly as it relates to lung cancer risk.[22] Because active smoking is a risk factor for bladder cancer, it may be possible that heavy exposure to sidestream smoke increases the risk of bladder cancer in nonsmokers. The possibility of a relationship between passive inhalation and bladder cancer receives some support from studies in which elevated levels of nicotine or cotinine (a metabolite of nicotine)[23–26] or mutagens[27] have been measured in the urine of nonsmokers passively exposed to smoke. The results of the current study did not suggest greater exposure to sidestream smoke among those with bladder cancer; however, information on passive inhalation was not available for all study subjects because of the use of a different questionnaire version early in the study. Furthermore, these questions provide only a rough estimate of current sidestream smoke exposure rather than of lifetime exposure. Future studies designed to obtain a more precise estimate of sidestream smoke exposure will be able to more clearly assess the relationship between exposure to others' smoke and the occurrence of bladder cancer.

Case-control studies that have examined the relationship of coffee consumption with bladder cancer have yielded inconsistent results. Morrison has recently reviewed these studies and concluded that the major problem in assessing the coffee–bladder cancer relationship is the difficulty of adequately controlling for confounding by cigarette smoking.[28] Of the three studies that present data on coffee consumption of nonsmokers separately, one showed little increased risk among nonsmokers,[29] one yielded an odds ratio of 1.9 for both men and women who drank 8 or more cups/week compared with drinkers of 7 or fewer cups/week,[30] and one showed an increased

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risk in men but not in women.[31] Although the current study found no association between coffee drinking and bladder cancer in nonsmokers of either sex, the disparate results in these studies leave the issue unresolved.

The finding in the current study of no apparent association between either diet beverage consumption or artificial sweetener use and bladder cancer in either sex is in agreement with the results of several other case-control studies.[13,32-36] Although a slight elevation in risk among women has been shown in subgroups of nonsmokers,[32,34,37] the results among men have been inconsistent.[34,37,38]

Snuff use has not been widely examined as a risk factor for bladder cancer. Dunham and colleagues[39] reported more snuff use among their white female controls (2.5%) than among cases (0.9%). The finding of the current study that cases were more likely to use snuff than controls must be interpreted with caution in view of the extremely small number of snuff users. The relationship between snuff use and bladder cancer should be examined further with more subjects.

The etiology of bladder cancer is still largely unknown. The current study, which has examined a number of potential risk factors in the absence of the confounding and interactive effects of the major risk factor (smoking), suggests that coffee drinking, artificial sweetener use, and exposure to sidestream smoke are not important factors in bladder cancer in nonsmokers.

REFERENCES

1. U. S. Department of Health and Human Services. The Health Consequences of Smoking: Cancer. A Report of the Surgeon General. DHHS Publication No. (PHS) 82-50179, Washington, DC: Public Health Service, Office on Smoking and Health, 1982; 101–113.
2. Matanowski GM, Elliot EA. Bladder cancer epidemiology. *Epidemiol Rev* 1981; 3:203–229.
3. Morrison AS, Cole P. Urinary tract. In: Schottenfeld D, Fraumeni T, eds. Cancer Epidemiology and Prevention. Philadelphia: W. B. Saunders, 1982; 925–937.
4. Doll R, Peto R. The Causes of Cancer. New York: Oxford University Press, 1981; 1221.
5. Cole P, Monson RR, Haning H, Friedell GH. Smoking and cancer of the lower urinary tract. *N Engl J Med* 1971; 284:129–134.
6. Wynder EL, Goldsmith R. The epidemiology of bladder cancer: A second look. *Cancer* 1977; 40:1246–1268.
7. Wynder EL, Stellman SD. Comparative epidemiology of tobacco-related cancers. *Cancer Res* 1977; 37:4608–4622.
8. U. S. Department of Commerce. U. S. Bureau of Census: Detailed Characteristics. Final Report, U. S. Summary. Publication No. PC(1)-D1, Washington, DC: U. S. Government Printing Office, 1973; Table 226.
9. Fleiss JL. Statistical Methods for Rates and Proportions, ed. 2. New York: John Wiley and Sons, 1981; 181–193.
10. Rothman KJ, Boice JD. Epidemiologic Analysis with a Programmable Calculator. Washington, DC: U. S. DHEW, Public Health Service Publication No. (NIH) 79-1649, 1979.
11. Wynder EL, Onderdonk S, Mantel N. An epidemiological investigation of cancer of the bladder. *Cancer* 1963; 16:1388–1407.
12. Cole P, Hoover R, Friedell GH. Occupation and cancer of the lower urinary tract. *Cancer* 1972; 29:1250–1260.
13. Najem GR, Louria DB, Seebode JJ *et al.* Lifetime occupation, smoking, caffeine, saccharine, hair dyes, and bladder carcinogenesis. *Int J Epidemiol* 1982; 11:212–217.
14. Howe GR, Burch JD, Miller AB *et al.* Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *J Natl Cancer Inst* 1980; 64:701–713.
15. Decoufle P, Stanislawczyk K, Houten L, Bross ID, Viadana E. A retrospective survey of cancer in relation to occupation. Washington, DC: U. S. Government Printing Office, DHEW Publication No. (NIOSH) 77-178, 1977.
16. Milham S. Occupational mortality in Washington State 1950–1970, vol. 1. Washington, DC: U. S. Government Printing Office, DHEW Publication No. (NIOSH) 76:175–176, 1976.
17. Higginson J. Proportion of cancers due to occupation. *Prev Med* 1980; 9:180–188.
18. Gottlieb MS, Pickle LW. Bladder cancer mortality in Louisiana. *J La State Med Soc* 1981; 133:6–9.
19. Miller CT, Neutel CI, Nair RC, Marrett LD, Last JM, Collins WE. Relative importance of risk factors in bladder carcinogenesis. *J Chronic Dis* 1978; 31:51–56.
20. Glashan RW, Cartwright RA. Occupational bladder cancer and cigarette smoking in West Yorkshire. *Br J Urol* 1981; 53:602–604.
21. Vineis P, Segnan N, Costa G, Terracini B. Evidence of a multiplicative effect between cigarette smoking and occupational exposures in the aetiology of bladder cancer. *Cancer Lett* 1981; 14:285–290.
22. Kabat GK, Wynder EL. Lung cancer in nonsmokers. *Cancer* 1984; 53:1214–1221.
23. Matsukura S, Taminato T, Kitano N *et al.* Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers: Evidence for passive smoking. *N Engl J Med* 1984; 311:828–832.
24. Greenberg RA, Haley NJ, Etzel RA, Loda FA. Measuring the exposure of infants to tobacco smoke: Nicotine and cotinine in urine and saliva. *N Engl J Med* 1984; 310:1075–1078.
25. Feyerabend C, Higenbottam T, Russell MAH. Nicotine concentrations in urine and saliva of smokers and non-smokers. *Br Med J* 1982; 284:1002–1004.
26. Russell MAH, Feyerabend C. Blood and urinary nicotine in non-smokers. *Lancet* 1975; 1:179–181.
27. Bos RP, Theuws JLG, Henderson PTH. Excretion of mutagens in human urine after passive smoking. *Cancer Lett* 1983; 19:85–90.
28. Morrison AS. Control of cigarette smoking in evaluating the association of coffee drinking and bladder cancer. In: MacMahon B, Sugimura T, eds. Coffee and Health, Banbury Report 17. Cold Spring Harbor Laboratory, 1984; 127–136.
29. Bross IDJ, Tidings J. Another look at coffee drinking and cancer of the urinary bladder. *Prev Med* 1973; 2:445–451.
30. Marrett LD, Walter SD, Meigs JW. Coffee drinking and bladder cancer in Connecticut. *Am J Epidemiol* 1983; 117:113–127.
31. Hartge P, Hoover R, West DW, Lyon JL. Coffee drinking and risk of bladder cancer. *J Natl Cancer Inst* 1983; 70:1021–1026.
32. Morrison AS, Buring JE. Artificial sweeteners and cancer of the lower urinary tract. *N Engl J Med* 1980; 302:537–541.
33. Silverman DT, Hoover RN, Swanson GM. Artificial sweeteners and lower urinary tract cancer: Hospital *vs.* population controls. *Am J Epidemiol* 1983; 117:326–334.
34. Hoover RN, Strasser PH. Artificial sweeteners and human bladder cancer: Preliminary results. *Lancet* 1980; 1:837–840.
35. Wynder EL, Stellman SD. Artificial sweetener use and bladder cancer: A case–control study. *Science* 1980; 207:1214–1216.
36. Kessler I. Non-nutritive sweeteners and human bladder cancer: Preliminary findings. *J Urol* 1976; 115:143–146.
37. Cartwright RA, Adib R, Glashan R, Gray BK. The epidemiology of bladder cancer in West Yorkshire: A preliminary report on non-occupational aetiologies. *Carcinogenesis* 1981; 2:343–347.
38. Miller AB, Howe GR. Artificial sweeteners and bladder cancer (letter). *Lancet* 1977; 2:1221–1222.
39. Dunham LJ, Rabson AS, Stewart HL, Frank AS, Young JL. Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans. *J Natl Cancer Inst* 1968; 41:683–709.

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RISK OF BLADDER CANCER BY SOURCE AND TYPE OF TOBACCO EXPOSURE: A CASE-CONTROL STUDY

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The association between tobacco use and risk of bladder cancer was investigated in a population-based case-control study conducted in Alberta and south-central Ontario, Canada, between 1979 and 1982. In all, 826 histologically-confirmed cancer cases and 792 randomly selected controls, individually matched to cases for age, sex, and area of residence, were recruited into the study. Compared to those who had never smoked cigarettes, males and females who had ever smoked cigarettes had a statistically highly significant 2-fold increase in risk of bladder cancer; for ex-smokers, the risk was intermediate between that for current smokers and never-smokers. There was a dose-dependent increase in risk of bladder cancer with total lifetime cigarette consumption, of similar magnitude for males and females. In males, risk increased with self-reported degree of inhalation in ex-smokers and in current smokers (statistically significant trend), while in females there was no association in current smokers, and a statistically significant inverse association in ex-smokers. Overall, risks of bladder cancer associated with lifetime consumption of plain and filter cigarettes were similar, and there was little evidence to suggest that switching from plain to filter cigarettes was beneficial. Neither passive smoking nor other forms of tobacco consumption (pipes, cigars, chewing tobacco, or snuff) were associated with altered risk of bladder cancer. The population attributable risk for cigarette smoking was about 47% in males and about 33% in females.

Epidemiologic studies of the relationship between tobacco use and bladder cancer have generally suggested that cigarette smoking is causally associated with increased risk, but have provided less conclusive evidence concerning the risk of bladder cancer associated with other forms of tobacco use and with passive smoking (Matanoski and Elliott, 1981; Najem *et al.*, 1982; Cartwright *et al.*, 1983; Mommsen and Aagard, 1983; Vineis *et al.*, 1984, 1988; Morrison *et al.*, 1984; Rebelakos *et al.*, 1985; Sandler *et al.*, 1985; Hartge *et al.*, 1985, 1987; Schifflers *et al.*, 1987; Kantor *et al.*, 1988). Therefore, there is a need for additional investigations of the last 2 issues, while several aspects of the association between cigarette smoking and bladder cancer also require further study, including the nature of the dose-response relationship, the relative magnitude of the effect in males and females, the influence of degree of inhalation, and the effects of different types of cigarettes (filter and non-filter). Of particular interest with respect to type of cigarette are the relative magnitude of the effects of plain (non-filter) and filter cigarettes, and the change in risk on switching from plain to filter cigarettes; large studies are needed to examine these issues and, to date, the only study in which both have been examined is that of Hartge *et al.* (1987), who observed that the risk of bladder cancer was higher for individuals who had smoked plain cigarettes only than for those who had smoked filter cigarettes only, but that changing from plain to filter cigarettes did not lead to a reduction in the risk of bladder cancer. In this paper, we examine the issues outlined above, using data from a large case-control study conducted in Canada.

SUBJECTS AND METHODS

The study methods have been presented in detail elsewhere (Risch *et al.*, 1988*a*) and are described here only briefly.

Cases and controls

Persons eligible for inclusion in the study as cases consisted of all individuals who were diagnosed between 1979 and 1982 with primary, histologically confirmed tumours of urothelial origin, who were resident in the province of Alberta, in metropolitan Toronto or in other parts of south-central Ontario, and who were between 35 and 79 years of age. The term "bladder cancer" as used here includes all bladder tumours of urothelial origin (whether of borderline or full malignancy) as well as all other primary malignant tumours of the bladder. (Patients with recurrent malignant neoplasms of the bladder or invasion of the bladder from primary prostatic cancer were not included.) Cases in northern Alberta were identified through the Cross Cancer Institute, while cases in southern Alberta were identified through the division of the province-wide tumour registry located in Calgary. In south-central Ontario, cases were identified by monthly review of records in hospital departments of surgery, urology, pathology, and of medical records. Of 1,251 eligible cases, 835 (67%) were interviewed, all within one year of diagnosis. Reasons for non-participation of potentially eligible cases (and controls) have been presented elsewhere (Risch *et al.*, 1988*a*).

Controls in both provinces were selected at random from province-wide, annually updated listings, and were matched one-to-one to cases for age (within 4 years), sex and area of residence. Of 1,483 potentially eligible controls, 792 (53%) agreed to participate; of these, 602 were male and 190 were female. By the end of the data collection period, matched controls had not been obtained for 43 cases. Also, interview data showed that errors in dates of birth invalidated the matching for 21 of the existing pairs. Nevertheless, it was possible to match the 21 controls from these last case-control pairs, and 55 of the 64 unmatched cases, either to each other or within the existing case-control pairs. Therefore, 781 matched sets were created, of which 739 were pairs, 35 were triplets, and 4, 2 and 1 comprised 4, 5 and 9 individuals, respectively. The 9 cases which could not be matched were deleted from the analyses; of the remaining cases, 627 were male and 199 were female.

Measurement of exposure

Information was obtained from study subjects by means of an interviewer-administered questionnaire which addressed family, medical, occupational and residential history, socio-economic factors, and intake of various dietary factors. Study

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subjects were also asked about their use of each of the following tobacco products: plain cigarettes, filter cigarettes, cigars, cigarillos, pipes, chewing tobacco and snuff. For each product for which ever use was reported, respondents were asked to indicate their level of consumption by age (*i.e.*, changes in the frequency of consumption with age were noted). These data enabled various indices of use (*e.g.*, total duration of use, years since last use) to be calculated. (Individuals with a lifetime cigarette consumption of less than 185 cigarettes were defined as never-smokers, while ex-smokers were defined as those who had last smoked more than 1 year prior to interview.) Study participants were then asked about the usual extent to which they inhaled the tobacco products that they had used (the options were "deeply", "somewhat", and "not at all"). Finally, they were asked about their exposure to the tobacco smoke of others at home and at work.

Statistical analysis

Conditional logistic regression models (Breslow and Day, 1980) were used to derive maximum likelihood odds ratio (OR) estimates and associated 95% confidence intervals (CI), and to test for the statistical significance of trends in risk. Matching was preserved for the majority of the analyses, but where the number of subjects available for analysis was small, matching was broken and unconditional logistic regression (Breslow and Day, 1980) was used. All of the estimates of effect presented here are adjusted for age (which was introduced into models at a continuous term, even when matching was retained). Additional adjustment for other risk factors for bladder cancer in this study [diabetes diagnosed after the age of 20 years (Risch *et al.*, 1988*a*) and several occupations (Risch *et al.*, 1988*b*)] did not substantially change the point estimates of effect, and the results presented here are derived from models which did not include these variables. The population attributable risk for cigarette smoking was calculated by the method of Bruzzi *et al.* (1985), using risk expressed in terms of log (1 + pack-years).

RESULTS

Several aspects of cigarette smoking history are examined in Table I, which shows little difference between the patterns for males and females. Compared to the risk of bladder cancer for those who had never smoked cigarettes, males and females who had ever smoked cigarettes had a statistically significant 2-fold increase in risk; risk for ex-smokers was intermediate between those for current smokers and for never-smokers. There was an inverse association between age at commencement of smoking and risk of bladder cancer, and some suggestion of increases in risk with duration of smoking and with average number of cigarettes smoked per day. Age at commencement of smoking and duration of smoking were inversely associated with each other, and when they were examined simultaneously (as continuous variables) in a conditional logistic regression model, only the effect for duration remained (data not shown). Duration and frequency of cigarette consumption were combined to give a measure of total lifetime cigarette consumption [expressed as pack-years *i.e.*, average frequency (packs/day) × duration (years)], and there was a positive association between this variable and risk of bladder cancer. A formal test for interaction between total cigarette

TABLE I - RISK OF BLADDER CANCER BY HISTORY OF CIGARETTE SMOKING[1]

Category	Males			Females		
	Number of cases	Number of controls	OR (95% CI)	Number of cases	Number of controls	OR (95% CI)
Never-smoked	61	112	1.0[2]	81	105	1.0[2]
Ever-smoked	566	490	2.08(1.47–2.93)	118	85	1.91(1.24–2.94)
Ex-smoker	287	305	1.67(1.16–2.41)	36	40	1.20(0.69–2.08)
Current smoker	279	185	2.65(1.82–3.86)	82	45	2.62(1.58–4.33)
Age first smoked (years)						
1–14	160	122	2.40(1.60–3.60)	13	7	2.42(0.91–6.39)
15–19	271	222	2.26(1.55–3.29)	50	28	2.66(1.42–4.99)
⩾20	135	146	1.63(1.09–2.43)	55	50	1.54(0.94–2.53)
p(trend)		0.025			0.044	
Duration of smoking (years)						
1–10	35	40	1.55(0.89–2.71)	9	16	0.76(0.29–1.99)
11–20	51	60	1.50(0.91–2.49)	11	13	1.14(0.47–2.81)
21–30	91	89	1.84(1.19–2.85)	29	12	3.36(1.44–7.87)
⩾31	389	301	2.34(1.63–3.39)	69	44	2.21(1.32–3.70)
p(trend)		<0.001			<0.001	
Average frequency of smoking (cigs./day)						
1–10	102	125	1.49(0.99–2.25)	36	41	1.22(0.69–2.15)
11–20	229	174	2.35(1.61–3.43)	46	27	2.30(1.24–4.28)
21–30	161	122	2.43(1.61–3.65)	36	17	2.88(1.47–5.63)
⩾31	74	69	1.95(1.22–3.10)	—	—	—[3]
p(trend)		<0.001			<0.001	
Pack-years of smoking						
1–19	131	162	1.47(0.99–2.19)	48	47	1.39(0.81–2.38)
20–39	184	141	2.36(1.59–3.50)	37	26	1.81(1.00–3.27)
⩾40	251	187	2.40(1.64–3.50)	33	12	4.88(2.11–11.27)
p(trend)		<0.001			<0.001	

[1]All cigarettes (plain and filter) combined. –[2]Reference category. Odds ratios are derived from matched analyses, and cannot be calculated directly from the unmatched distribution of cases and controls shown in the Table. –[3]Examined at 4 levels only, the uppermost level being more than 20 cigarettes/day.

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consumption and sex was not statistically significant (p = 0.13); similarly, there was no interaction between total cigarette consumption and age (p = 0.33).

A more formal examination of the dose-response relationship is presented in Table IIA (results in the body of this table are for males and females combined). In model I, average frequency and duration were entered as simple linear terms. Both factors had statistically significant positive associations with risk of bladder cancer, and there was no evidence of an interaction between them. Ex-smokers were at reduced risk in relation to current smokers, for a given frequency and duration of use. In the second model in Table IIA, risk was expressed on a logarithmic scale as a function of total cigarette consumption [*i.e.*, log (1 + [average frequency × duration])], and a term for ex-smokers was included in the model. The fit of this model to the data was slightly better than that of model I and, since it employed fewer parameters, it was used to represent the effect of cigarette smoking in subsequent analyses. In general, however, the 2 models give similar predictions of risk (Table IIB). When the analyses were repeated for males and females separately, the results were similar, except for heavy exposures, where risks for females were somewhat higher than the corresponding risks for males (data not shown).

As indicated in Table IIA, those who gave up cigarette smoking were at a lower risk than those who continued to smoke, given the same frequency and duration of cigarette smoking. This effect was examined further by subdividing ex-smokers by time since quitting (Table III). The reduction in risk experienced by ex-smokers appeared to be greatest in the first decade after quitting.

Risk of bladder cancer increased with self-reported degree of inhalation in male cigarette smokers, and decreased in females (Table IV); the latter trend was statistically significant. In males, risk increased with degree of inhalation in both ex- and current smokers [when both categorized variables were introduced into a conditional logistic regression model together with the term log (1 + cumulated pack-years)], and the trend for current smokers was statistically significant. In females, there was an inverse association (statistically significant) between degree of inhalation and risk of bladder cancer in ex-smokers, while the variation in risk with degree of inhalation in current smokers was irregular and not dose-dependent (data not shown).

Risk of bladder cancer increased with lifetime cumulative consumption of both plain and filter cigarettes. This is shown in Table V, which reveals the similarity of risks for the 2 types of cigarettes at corresponding levels of cumulative consumption (although the data shown in the footnote to Table V suggest that the effect of filter cigarettes was slightly stronger than that of plain cigarettes).

There was little evidence to suggest that switching from plain to filter cigarettes conferred benefit in terms of reduction in the risk of bladder cancer (Table VI). Indeed, the risk for subjects who had switched from plain to filter cigarettes was generally higher than that for subjects who had smoked plain cigarettes only.

Risk of bladder cancer was not influenced by the use of pipes, cigars, chewing tobacco or snuff (Table VII). With analyses restricted to subjects who had never smoked cigarettes, the results were practically the same (data not shown).

Table VIII shows results relating to reported exposure to passive smoking. There was no evidence for an effect of passive smoking, even when risk was examined by duration of exposure, and when those who had been exposed both at work and at home were compared with those reporting no exposure (data not shown). Also, passive smoking was not associated with altered risk of bladder cancer in subjects who had not smoked cigarettes (data not shown).

The population-attributable risk for cigarette smoking was about 47% in males, and about 33% in females. For males and females combined, the population-attributable risk for cigarette smoking was about 44%.

DISCUSSION

Potential sources of bias in this study have been discussed in detail elsewhere (Risch *et al.*, 1988*a*), and are reviewed here only briefly. Firstly, the response rate for cases was 67% in both areas of the study, the major reasons for non-participation being subject refusal (14%) and death or severe illness (11%);

TABLE II - DOSE-RESPONSE MODELS AND PREDICTIONS OF THE EFFECT OF CIGARETTE SMOKING[1]

IIA. Dose-response models

Model	Variable	Coefficient	Standard error	p value
I	Average frequency (packs/day)	0.5178	0.2221	0.020
	Duration (years)	0.01806	0.004389	<0.0001
	Average frequency × duration	−0.009889	0.006193	0.11
	Ex-cigarette smoker	−0.2961	0.1258	0.019
II	Log (1 + [average frequency (packs/day) × duration (years)])	0.2396	0.03564	$<10^{-10}$
	Ex-cigarette smoker	−0.2910	0.1112	0.0089

IIB. Predictions of effect

Average frequency (cigs/day)	Duration (years)	Relative risk[2] Model I	Model II
20	20	1.98	2.07
20	40	2.35	2.44
40	20	2.72	2.44
40	40	2.63	2.87

[1]Coefficients shown in the body of the Table are for males and females combined. For males, the coefficients for frequency, duration, frequency × duration, and log (1 + (frequency × duration)), were 0.4925, 0.01919, −0.01079, and 0.2190, respectively; for females, the corresponding coefficients were 0.3270, 0.001742, 0.01840, and 0.3209, respectively. [2]Risk relative to lifetime non-cigarette smokers for current cigarette smokers of same age and sex.

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TABLE III - RISK OF BLADDER CANCER IN CURRENT SMOKERS, AND IN EX-SMOKERS BY YEARS SINCE LAST SMOKED

Category	Males			Females		
	Number of cases	Number of controls	OR[1](95% CI)	Number of cases	Number of controls	OR[1](95% CI)
Never smoked	61	112	1.0[2]	81	105	1.0[2]
Ex-smokers, by years since last smoked:						
>10	68	53	1.37(0.68–2.75)	15	8	0.83(0.19–3.69)
>5 and ≤10	40	54	0.79(0.37–1.65)	7	5	0.69(0.12–4.12)
>1 and ≤5	179	198	1.10(0.64–1.88)	14	27	0.42(0.15–1.16)
Current smokers	279	185	1.55(0.80–2.98)	82	45	0.98(0.29–3.39)
p(trend)[3]		0.16			0.090	

[1]Adjusted for lifetime cigarette consumption [log (1 + cumulated pack-years)].–[2]Reference category. Odds ratios for all subjects are derived from matched analyses and cannot be calculated directly from the unmatched distributions of cases and controls shown in the Table.–[3]For years since last smoked as a continuous variable.

TABLE IV - RISK OF BLADDER CANCER IN CIGARETTE SMOKERS, BY DEGREE OF INHALATION

Category	Males			Females		
	Number of cases	Number of controls	OR (95% CI)	Number of cases	Number of controls	OR (95% CI)
Never smoked	61	112	1.0[1]	81	105	1.0[1]
Ever smoked, and inhaled:						
Not at all	49	57	1.14(0.67–1.96)	28	19	0.90(0.37–2.21)
Somewhat	178	159	1.36(0.85–2.18)	56	35	0.68(0.29–1.61)
Deeply	339	274	1.47(0.91–2.38)	34	31	0.36(0.13–0.97)
p(trend)		0.11			0.028	

[1]Reference category. Odds ratios are derived from matched analyses and cannot be calculated directly from the unmatched distribution of cases and controls shown in the Table. Estimates of effect are adjusted for lifetime cigarette consumption [log (1 + cumulated pack-years)].

for controls, the response rate was 69%. The results presented here may be biased through non-response, although this would have occurred only if response rates by smoking status were different for cases and controls. Secondly, of the 826 cases included in these analyses, 64 had tumours of borderline malignancy, while virtually all of the remaining tumours were classified as transitional-cell or papillary transitional-cell carcinomas. When the analyses were repeated after excluding the 64 cases of borderline malignancy (and their corresponding controls), the results were similar to those presented here. Thirdly, cases and controls may have been misclassified with respect to exposure status, which was determined from interviewer-administered questionnaires. Although some misclassification seems likely, there is little reason to suspect that there were marked differences between cases and controls in the degree of misclassification.

In this study, males and females who had ever smoked cigarettes had a statistically significant 2-fold increase in risk of bladder cancer. The risk for ex-smokers was intermediate between those for current smokers and for never-smokers, and

TABLE V - RISK OF BLADDER CANCER BY LIFETIME CUMULATIVE CONSUMPTION OF PLAIN AND FILTER CIGARETTES[1]

Category	Males			Females		
	Number of cases	Number of controls	OR (95% CI)	Number of cases	Number of controls	OR (95% CI)
Plain cigarettes (pack-years)						
0	126	173	1.0[2]	127	140	1.0[2]
>0 and ≤10	143	146	1.23(0.87–1.75)	35	34	0.95(0.54–1.70)
>10 and ≤25	158	124	1.61(1.13–2.30)	24	12	1.49(0.65–3.41)
>25	200	159	1.72(1.24–2.40)	13	4	2.88(0.85–9.72)
p(trend)		0.013			0.035	
Filter-cigarettes (pack-years)						
0	245	301	1.0[2]	92	116	1.0[2]
>0 and ≤10	100	107	1.14(0.81–1.61)	27	24	1.21(0.59–2.50)
>10 and ≤25	125	91	1.56(1.12–2.16)	43	30	1.68(0.94–3.00)
>25	157	103	1.99(1.43–2.79)	37	20	2.36(1.15–4.84)
p(trend)		5.6×10^{-5}			7.0×10^{-4}	

[1]With lifetime cumulative consumption examined as a continuous variable [i.e., log (1 + total consumption)], the increase in risk with each 10 pack-years of use of plain cigarettes was 1.31 (95% CI 1.11–1.55) for males, and 1.52 (0.91–2.56) for females; the corresponding estimates for use of filter cigarettes were 1.53 (1.28–1.83) and 1.84 (1.23–2.74), respectively.–[2]Reference category. Odds ratios are derived from matched analyses and cannot be calculated from the unmatched distributions of cases and controls shown in the Table.

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TABLE VI - RISK OF BLADDER CANCER BY SMOKING STATUS AND BY TYPE OF CIGARETTE EVER SMOKED

Category	Number of cases	Number of controls	OR (95% CI)
Current smokers			
Plain only	42	35	1.0[1]
Switched to filter[2]	174	110	1.36(0.80–2.33)
<15 years ago			
Switched to filter	79	38	1.88(1.00–3.53)
≥15 years ago			
Filter only	66	47	1.35(0.71–2.56)
Ex-smokers, quit			
<10 years ago			
Plain only	30	29	0.86(0.42–1.75)
Switched to filter	73	72	0.93(0.52–1.64)
Filter only	27	19	1.36(0.62–2.99)
Ex-smokers, quit			
≥10 years ago			
Plain only	123	136	0.97(0.56–1.68)
Switched to filter	52	59	0.91(0.49–1.70)
Filter only	18	30	0.67(0.31–1.47)
Never smoked	142	217	0.98(0.48–2.02)

[1]Reference category. Odds ratios are derived from matched analyses and cannot be calculated from the unmatched distribution of cases shown in the Table. Estimates are adjusted for log (1 + cumulated pack-years). [2]In the categories in which subjects reported switching to filter cigarettes, there were (reading from the first mentioned "switching" category to the last) 3, 5, 5 and 5 cases, respectively, and 2, 0, 3 and 4 controls, respectively.

TABLE VII - RISK OF BLADDER CANCER (IN MEN) ASSOCIATED WITH EVER USE OF PIPES, CIGARS, CHEWING TOBACCO AND SNUFF

Category	Number of cases	Number of controls	OR (95% CI)
Pipe			
Never smoked	485	469	1.0[1]
Ever smoked	142	133	1.03(0.77–1.37)
Cigars			
Never smoked	561	529	1.0[1]
Ever smoked	66	73	0.97(0.69–1.36)
Chewing tobacco			
Never used	601	568	1.0[1]
Ever used	26	34	0.60(0.34–1.06)
Snuff			
Never used	618	584	1.0[1]
Ever used	9	18	0.47(0.21–1.07)

[1]Reference category. Odds ratios are derived from matched analyses and cannot be calculated directly from the unmatched distribution of cases and controls shown in the Table. All estimates of effect are adjusted for lifetime cigarette consumption (log (1 + cumulated pack-years)).

the reduction in risk associated with giving up smoking was greatest in the first decade after quitting. There was some suggestion of an increase in risk with duration and with average frequency of cigarette smoking, and there was a dose-dependent increase in risk of bladder cancer with total lifetime cigarette consumption (*i.e.*, average frequency × duration).

These results are in broad agreement with those of other recent case-control studies of bladder cancer (Najem *et al.*, 1982; Cartwright *et al.*, 1983; Mommson and Aagard, 1983; Vineis *et al.*, 1984; Morrison *et al.*, 1984; Rebelakos *et al.*, 1985; Hartge *et al.*, 1987; Kantor *et al.*, 1988), in which at least some aspects of the association with cigarette smoking have been examined. The consistency of these findings, together with the strength of the association (the relative risk for ever-smokers ranges from about 2 to 5), the dose-response nature of the relationship, the persistence of the association after adjustment for major potential sources of confounding, and its biological plausibility (Wynder and Goldsmith, 1977), strongly suggest that the association is causal. The apparent decrease in risk of bladder cancer on cessation of cigarette smoking suggests a late-stage carcinogenic effect, although the presence of cigarette smoke of compounds capable of inducing bladder cancer in animal experiments (Wynder and Goldsmith, 1977) raises the possibility of an early-stage effect in addition.

For males in this study, risk of bladder cancer increased with self-reported degree of inhalation, and the association was statistically significant in current smokers; in contrast, there was a statistically significant inverse association between degree of inhalation and risk of bladder cancer in female ex-smokers. Morrison *et al.* (1984), in a multi-centre case-control study, observed in each centre a small increase in risk of bladder cancer in male cigarette smokers who inhaled deeply; for females, risk was either increased or decreased, but not significantly so. Although the findings for males seem plausible, the results for females raise doubts about the validity of self-reported degree of inhalation. Stepney (1982), who compared biochemical measures of exposure to cigarette smoke with self-reported degree of inhalation in a group of smokers, concluded that self-reports provided little indication of actual exposure to toxic constituents of smoke, and suggested that this resulted from failure to obtain information on an additional dimension of inhalation, namely its duration. Data on duration of inhalation were not available in the present study, and were not reported by Morrison *et al.* (1984).

The increase in risk with each 10 pack-years of use of filter cigarettes was about 15% higher than that for plain cigarettes. The reason for the stronger effect of filter cigarettes is not clear, but possible explanations include chance, and variation in the effect of cigarette smoking with age (subjects who had smoked filter cigarettes were generally younger than those who had smoked plain cigarettes). Of these, the latter can probably be excluded, since there was no statistical evidence for an age interaction. In contrast to the results of this study, previous comparisons of the risk of bladder cancer associated with use of plain and filter cigarettes have mostly suggested a stronger effect for the former. Thus, Howe *et al.* (1980) and Vineis *et al.* (1984) observed higher risks for users of plain cigarettes, while Cartwright *et al.* (1983) and Hartge *et al.* (1987) reported higher risks of bladder cancer for subjects who had smoked unfiltered cigarettes only than for those who had smoked filtered cigarettes only; in contrast, Morrison *et al.* (1984) found no difference in risk between smokers of filter and plain cigarettes.

This study provided little evidence to suggest that switching from plain to filter cigarettes was beneficial. Hartge *et al.* (1987) (whose analysis we replicated) obtained similar results, while Cartwright *et al.* (1983) observed that the risk of bladder cancer for individuals who had smoked both plain and filter cigarettes was increased, and of similar magnitude to the increase in risk for subjects who had smoked plain cigarettes only. Since filter cigarettes were introduced only in the late 1950s, at the time of our study they had been available for about 20 years. If filter cigarettes have an early-stage carcinogenic effect, then given that the latent interval between exposure to tobacco smoke and development of bladder cancer may be of the order of 20 years or more, it is possible that insufficient time has elapsed to allow the full spectrum of their effects to emerge, and this may account for the apparently paradoxical findings to date.

Other forms of tobacco use (pipes, cigars, chewing tobacco and snuff) were not associated with increased risk of bladder cancer in our study; absence of associations for chewing tobacco and snuff may reflect the small numbers of individuals who reported ever having used these substances. Previous studies have also provided little support for an effect on non-cigarette tobaccos (Matanoski and Elliott, 1981), although 3

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TABLE VIII – RISK OF BLADDER CANCER BY HISTORY OF PASSIVE SMOKING

Category	Males			Females		
	Number of cases	Number of controls	OR[1](95% CI)	Number of cases	Number of controls	OR[1](95% CI)
All subjects						
Exposed to smoke of others at home:						
No	123	144	1.0[2]	28	19	1.0[2]
Yes	504	458	1.19(0.88–1.61)	171	171	0.63(0.33–1.21)
Exposed to smoke of others at work:						
No	337	326	1.0[2]	117	114	1.0[2]
Yes	290	276	0.98(0.78–1.24)	82	76	0.87(0.57–1.35)
Non-smokers only[3]						
Exposed to smoke of others at home:						
No	24	40	1.0[2]	15	15	1.0[2]
Yes	37	72	0.94(0.45–1.95)	66	90	0.75(0.33–1.71)
Exposed to smoke of others at work:						
No	36	67	1.0[2]	55	67	1.0[2]
Yes	25	45	0.97(0.50–1.91)	26	38	0.93(0.48–1.79)

[1]Adjusted for lifetime cigarette consumption [log (1 + cumulated pack-years)].–[2]Reference category. Odds ratios for all subjects are derived from matched analyses and cannot be calculated directly from the unmatched distributions of cases and controls shown in the Table.–[3]Odds ratios for non-smokers only are derived from unconditional logistic regression analyses (adjusted for age in 4 categories, study location in 4 categories, and their interactions).

subgroups of pipe smokers have been reported to have an increased risk of bladder cancer: those who have never smoked cigarettes (Morrison *et al.*, 1984), those who inhale deeply (Howe *et al.*, 1980), and those who have never smoked cigarettes and who inhale deeply (Hartge *et al.*, 1985). Despite the plausibility of associations between cigar and pipe smoking and risk of bladder cancer [since the smoke of both types of tobacco contains many of the same substances as that of cigarette tobacco (Hartge *et al.*, 1985)], it has been suggested that their effect is likely to be small (Morrison *et al.*, 1984), which presumably accounts for the inconclusive nature of findings to date.

Mutagens have been detected in the urine of passive smokers (Bos *et al.*, 1983). Therefore, it seems plausible to suggest that individuals exposed to environmental tobacco smoke might be at increased risk of bladder cancer. However, given that the association between passive smoking and lung cancer appears to be relatively weak (Fielding and Phenow, 1988), it does not seem likely that any association between passive smoking and bladder cancer will be strong. Thus, the absence of an association in this study, and in the smaller study of Sandler *et al.* (1985), is not surprising.

In summary, the results of our study provide strong support for a causal relationship between cigarette smoking and the occurrence of bladder cancer. Furthermore, they suggest that switching from plain to filter cigarettes does not reduce risk, and provide little support for effects of other forms of tobacco use or for passive smoking. From this study it can be estimated that about 47% of bladder cancer in males, and about 33% of that in females, can be accounted for by cigarette smoking. Thus, further attempts should be made to identify the remaining contributors to bladder cancer risk, particularly in females.

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REFERENCES

Bos, R.P., Theuws, J.L.G. and Henderson, P.T., Excretion of mutagen in human urine after passive smoking. *Cancer Lett.*, **19**, 85–90 (1983).

Breslow, N.E. and Day, N.E., Statistical methods in cancer research. Vol. I. The analysis of case-control studies. *IARC Scientific Publications*. 32, IARC, Lyon (1980).

Bruzzi, P., Green, S.B., Byar, D.P., Brinton, L.A. and Schairer, C., Estimating the population attributable risk for multiple risk factors using case-control data. *Amer. J. Epidemiol.*, **122**, 904–914 (1985).

Cartwright, R.A., Adib, R., Appleyard, I., Glashan, R.W., Gray, B., Hamilton-Stewart, P.A., Robinson, M. and Barham, D., Cigarette smoking and bladder cancer: an epidemiological inquiry in West Yorkshire. *J. Epidemiol. Commun. Hlth.* **37**, 256–263 (1983).

Fielding, J.E. and Phenow, K.J., Health effects of involuntary smoking. *N. Engl. J. Med.*, **319**, 1452–1460 (1988).

Hartge, P., Hoover, R. and Kantor, A., Bladder cancer risk and pipes, cigars, and smokeless tobacco. *Cancer*, **55**, 901–906 (1985).

Hartge, P., Silverman, D., Hoover, R., and 15 others, Changing cigarette habits and bladder cancer risk: a case-control study. *J. nat. Cancer Inst.* **78**, 1119–1125 (1987).

Howe, G.R., Burch, J.D., Miller, A.B., Cook, G.M., Esteve, J., Morrison, B., Gordon, P., Chambers, L.W., Fodor, G., and Winsor, G.M., Tobacco use, occupation, various nutrients, and bladder cancer. *J. nat. Cancer Inst.*, **64**, 701–713 (1980).

Kantor, A.F., Hartge, P., Hoover, R.N. and Fraumeni, J.F., Jr., Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. *Cancer Res.*, **48**, 3853–3855 (1988).

Matanoski, G.M. and Elliott, E.A., Bladder cancer epidemiology. *Epidemiol. Rev.*, **3**, 203–229 (1981).

2023382051

Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

MOMMSEN, S. and AAGARD, J., Tobacco as a risk factor in bladder cancer. *Carcinogenesis*, **4**, 335–338 (1983).

MORRISON, A.S., BURING, J.E., VERHOEK, W.G., AOKI, K., LECK, I., OHNO, Y. and OBATA, K., An international study of smoking and bladder cancer. *J. Urol.*, **131**, 650–654 (1984).

NAJEM, G.R., LOURIA, D.B., SEEBODE, J.J., THIND, I.S., PRUSAKOWSKI, J.M., AMBROSE, R.B. and FERNICOLA, A.R., Life-time occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. *Int. J. Epidemiol.*, **11**, 212–217 (1982).

REBELAKOS, A., TRICHOPOULOS, D., TZONOU, A., ZAVITSANOS, X., VELONAKIS, E. and TRICHOPOULOS, A., Tobacco smoking, coffee drinking, and occupation as risk factors for bladder cancer in Greece. *J. nat. Cancer Inst.*, **75**, 455–461 (1985).

RISCH, H.A., BURCH, J.D., MILLER, A.B., HILL, G.B., STEELE, R. and HOWE, G.R., Dietary factors and the incidence of cancer of the urinary bladder. *Amer. J. Epidemiol.*, **127**, 1179–1191 (1988*a*).

RISCH, H.A., BURCH, J.D., MILLER, A.B., HILL, G.B., STEELE, R. and HOWE, G.R., Occupational factors and the incidence of cancer of the bladder in Canada. *Brit. J. indust. Med.*, **45**, 361–367 (1988*b*).

SANDLER, D.P., EVERSON, R.B. and WILCOX, A.J., Passive smoking in adulthood and cancer risk. *Amer. J. Epidemiol.*, **121**, 37–48 (1985).

SCHIFFLERS, E., JAMART, J. and RENARD, V., Tobacco and occupation as risk factors in bladder cancer: a case-control study in southern Belgium. *Int. J. Cancer*, **39**, 287–292 (1987).

STEPNEY, R., Are smokers' self-reports of inhalation a useful measure of smoke exposure? *J. Epidemiol. Commun. Hlth.* **36**, 109–112 (1982).

VINEIS, P., ESTÈVE, J. and TERRACINI, B., Bladder cancer and smoking in males: types of cigarettes, age at start, effect of stopping and interaction with occupation. *Int. J. Cancer*, **34**, 165–170 (1984).

VINEIS, P., ESTÈVE, J., HARTGE, P., HOOVER, R., SILVERMAN, D.T. and TERRACINI, B., Effects of timing and type of tobacco in cigarette-induced bladder cancer. *Cancer Res.*, **48**, 3849–3852 (1988).

WYNDER, E.L. and GOLDSMITH, R., The epidemiology of bladder cancer A second look. *Cancer*, **40**, 1246–1268 (1977).

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PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK[1]

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Overall cancer risk from adult passive smoking has been examined using smoking by spouse as the measure of exposure. Information on smoking by spouse was obtained for 518 cancer cases and 518 noncancer controls. Cancer cases were identified from a hospital-based tumor registry in North Carolina. Cases included all sites except basal cell cancer of the skin and were between the ages of 15 and 59 years at the time of diagnosis. Cancer risk among individuals ever married to smokers was 1.6 times that among those never married to smokers ($p < 0.01$). This increased risk was not explained by confounding by individual smoking habits, demographic characteristics, or social class. Elevated risks were seen for several specific cancer sites and were not limited to lung cancer or other "smoking-related" tumors. Risks from passive smoking appeared greater among groups generally at lower cancer risk (females, nonsmokers, and individuals younger than age 50 years), but were not limited to these groups.

neoplasms; risk; smoking; tobacco smoke pollution

Passive exposure to cigarette smoke has been linked with a variety of health consequences in humans, including bronchitis and pneumonia in infants (1), reduced pulmonary function (2) and acute respiratory disease in children (3–5), and decreased airway function in otherwise healthy adults (6). Several reports have also focused attention on a possible association between passive exposure to cigarette smoke and lung cancer (7–10).

In a case-control study by Trichopoulos and colleagues (7), 51 white females with lung cancer and 163 controls from an orthopedic service were compared with regard to smoking histories of husbands. Women who were not smokers but were married to smokers were at two- to threefold risk for lung cancer compared with nonsmoking women who were not married to smokers. An updated report of this study involving 77 nonsmoking lung cancer cases and 225 nonsmoking controls confirmed the twofold risk among passive smokers (8). In a prospective study from Japan, Hirayama (9) observed 245 lung cancer deaths among 91,000 married women. The lung cancer death rate for nonsmoking women married to smokers was nearly twice that for nonsmoking women married to nonsmokers and was one-half that for women who themselves smoked. Emphysema was the only other cause of death to exhibit such a pattern, although the trend was not statis-

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tically significant. Most recently, Correa et al. (10) reported a twofold risk for lung cancer among nonsmokers married to smokers. In contrast, analysis of data from an American Cancer Society study in the United States failed to demonstrate an association between passive exposure to cigarette smoke and lung cancer risk (11).

Many of the constituents of mainstream cigarette smoke which is actively inhaled by the smoker are present in reduced quantity in exhaled smoke (12) which is then passively inhaled by the nonsmoker. These same constituents are also contained in sidestream smoke which is released from the cigarette between active puffs and is also inhaled by the passive smoker. One might expect to find, as did Hirayama (9) for lung cancer, that for smoking-related sites, the cancer risk in individuals passively exposed to cigarette smoke might fall between that for smokers and that for nonsmokers. Risk from passive smoking might also be expected to be much lower than that from direct smoking.

However, some chemicals appear in higher concentration in sidestream smoke than in mainstream smoke, making the exposure from passive smoking qualitatively different (12, 13). The health consequences from passive smoking may, therefore, differ from those of direct smoking. These chemicals, many of which are known carcinogens, might lead to increased risk for cancer at sites not shown to be related to direct exposure to cigarette smoke. In comparing sidestream with mainstream smoke, Brunnemann (in refs. 12 and 13) found 52 times as much dimethylnitrosamine, 16 times as much naphthalene, 28 times as much methylnaphthalene, 3.4 times as much benzo(*a*)pyrene, and 5.6 times as much toluene, for example, in sidestream smoke as in mainstream smoke. While the concentrations of these chemicals are higher than in mainstream smoke, actual exposure from passive smoking is heavily influenced by the amount of smoke generated, the volume of ambient air, room ventilation, and the manner in which the cigarettes are smoked.

Differences in the route of inhalation of sidestream and mainstream smoke might also account for differences in site-specific effects. Wynder and Goodman (14), for example, have proposed that if sidestream smoke components are inhaled through the nasal passages, gaseous components but not smoke particulates would reach the lung.

As a preliminary exploration of the hypothesis that passive exposure to cigarette smoke may be carcinogenic, we examined adult passive exposure to cigarette smoke in relationship to cancers of all sites. Since active and passive smokers may differ in the mix of carcinogens to which they are exposed, it is not obvious which sites might be at highest risk of cancer among passive smokers. Since active smokers are also passively exposed, candidate sites might be drawn from those that have been linked with active smoking. However, there may be additional sites whose relationship to smoking has been obscured. In studies comparing smokers with nonsmokers, passive smokers are often included in the nonsmoking group. This would make it difficult to detect small differences in risk due to passive smoking. We report here on cancer risk from passive smoking using smoking histories of spouses as a measure of passive exposure to cigarette smoke during adulthood.

METHODS

Data reported here are from a study of childhood exposure to cigarette smoke and cancer risk in adulthood (29). Cases for study were selected from the hospital-based tumor registry at the North Carolina Memorial Hospital of the University of North Carolina in Chapel Hill. They included all cases diagnosed between July 1, 1979 and March 31, 1981 and assumed to be alive as of March 31, 1981. Cases were between the ages of 15 and 59 years at the time of diagnosis and included all cancer sites ex-

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cept basal cell cancer of the skin. Cases were restricted to this age group to maximize the likelihood of also detecting effects from childhood exposure to cigarette smoke. Individuals older than 60 years in 1981 are not likely to have had mothers who smoked. Patients with multiple primary tumors were included only if the first primary tumor was diagnosed during the study period.

Cases were mailed a questionnaire for self-completion. This mailing was followed by a second mailing and then a telephone call if needed. In addition to questions on exposure to cigarette smoke, cases were asked to identify friends or acquaintances who did not have cancer to serve as comparison subjects. These friends were the same race, sex, and age (±5 years) as the cases. Approximately 60 per cent of the controls were identified in this manner. For cases for whom friend controls were not successfully obtained, population controls were identified by systematic telephone sampling. Beginning with the telephone numbers of the cases, the next higher or lower telephone numbers were called until individuals of the same race, sex, and age (±5 years) were found. For cases interviewed by telephone, the calls to identify controls were made at the same time of day. For cases contacted by mail, telephone controls were chosen during randomly assigned times of day.

Of 740 eligible cancer cases identified from the tumor registry, 107 (14 per cent) died before we could contact them. An additional 115 (15 per cent) either refused (n = 71) to participate or could not be contacted. In all, completed questionnaires were obtained for 518 (70 per cent) of the eligible cases.

Of 518 cases, 360 (70 per cent) named friends or acquaintances who could be contacted as controls. Of these, 86 per cent were successfully contacted for an overall response rate of 60 per cent. To obtain the additional 209 controls, 1,237 households were telephoned. Screening data (age, race, sex, and cancer history of household members) were obtained for 988 households (80 per cent); 224 (23 per cent) of these households had a qualifying member. Fifteen (7 per cent) qualifying telephone controls refused to participate. The overall response rate for selection of telephone controls was 75 per cent (80 per cent × 93 per cent). Although not shown here, data were analyzed separately by control selection group, and the adjusted results were identical to those obtained when the control groups were combined.

Procedurally, the control selection process involved one-to-one matching. This was done to allow the selection of population controls without having an enumerated sampling frame. The analyses presented here are for unmatched data to maximize the study sample size following losses due to missing data on exposure. In most comparisons, the factors used in control selection are taken into account by adjustment procedures. Parallel analyses for matched pairs were carried out. Although not presented here, the results were similar.

Passive exposure to cigarette smoke during adulthood was estimated from a questionnaire report of the number of years of marriage during which a spouse smoked. Subjects were considered exposed if they had a spouse who smoked regularly at any time during their marriage. Regular smoking was defined as smoking at least one cigarette per day for as long as six months. The nonexposed group consisted of persons married to nonsmokers and persons who never married. The quantity smoked was reported as the average number of cigarettes smoked per day by a spouse while married to a study subject.

For the analysis of questionnaire data, odds ratios were calculated, and the chi-square test was used to assess statistical significance. Combined estimates of the odds ratio (OR) in stratified analyses were obtained using the Mantel-Haenszel technique (15). The method of Gart (16) was used to obtain 95 per cent confidence limits

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for the combined estimates of the odds ratio. When the 95 per cent confidence limits did not include unity, the odds ratio was considered statistically significant ($p < 0.05$). Level of education was reported as number of years of school completed and occupation was given as usual occupation. For stratified and adjusted analyses, age and level of education were treated as categorical variables with four levels of age (<30, 30–39, 40–49, and 50+ years) and three levels of education (<12 years, 12 years, and >12 years).

Results

The distribution of cases by cancer site is shown in table 1. The young age of cases, the referral nature of the hospital, and the fact that the study was limited to living cases account for the distribution of cancers seen. There was a predominance of breast cancers, female genital tract cancers, and leukemia and lymphoma, and a relative lack of respiratory tumors. Eligible cases with respiratory cancer were significantly more likely to die before they could be contacted for this study.

Cases and controls are compared in table 2. Cases and controls are, by design, distributed similarly by race and sex, with 70 per cent of each group white and 67 per cent female. The mean age of cases (43.6 years) and controls (43.5 years) is also similar. Level of education differs significantly between groups; 45 per cent of cases and 36 per cent of controls never graduated from high school. Level of education, therefore, is taken into consideration in most analyses. On the other hand, cases and controls do not differ by broad occupational category. A greater proportion of controls never married (16 per cent vs. 13 per cent), but this difference is not statistically significant. Cancer cases and controls also do not differ in reported smoking histories. In part this is due to the relative absence of lung cancer cases and to the method of control selection. Sixty per cent of controls are friends of cases, and the smoking habits of individuals who are friends may be similar. When only cases with population controls are included, 57 per cent of cases and 46 per cent of population controls were smokers.

The overall crude cancer risk for individuals ever married to smokers is 1.6 times that for those not married to smokers ($p < 0.01$) (table 3). Adjusting independently

Table 1

Distribution of cancer cases by site of primary tumor and study status

Site	ICD† No.	Included		Refused or lost	
		No.	(%)	No.	(%)
Lip, oral cavity, and pharynx	140–149	22	(4)	15	(7)
Digestive organs and peritoneum	150–159	41	(8)	16	(7)
Respiratory and intrathoracic organs	160–165	32	(6)	43	(19)*
Bone, connective tissue, and skin	170–173	42	(8)	13	(6)
Breast	174	60	(12)	16	(7)
Female genital organs	179–184	175	(34)	61	(28)
Prostate	185	10	(2)	0	(0)
Testis	186	6	(1)	3	(1)
Urinary tract	188, 189	6	(1)	9	(4)
Eye, brain, and other nervous system	190–192	38	(7)	20	(9)
Thyroid and other endocrine glands	193, 194	27	(5)	3	(1)
Lymphatic and hematopoietic tissue	200–207	52	(10)	13	(6)
Site unspecified	199	7	(1)	10	(5)
All sites		518	(100.0)	222	(100.0)

* $p < 0.01$.

† ICD, *International Classification of Diseases*, Ninth Revision.

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TABLE 2

Comparison of cases and controls

Factor	Cases	Controls
	No. (%)	No. (%)
Total	518 (100)	518 (100)
Age		
<30	96 (19)	99 (19)
30–39	89 (17)	105 (20)
40–49	132 (25)	121 (23)
50+	201 (39)	193 (37)
Race		
Nonwhite	153 (30)	153 (30)
White	365 (70)	365 (70)
Sex		
Male	169 (33)	169 (33)
Female	349 (67)	349 (67)
Marital status*		
Never married	65 (13)	79 (16)
Ever married	444 (87)	410 (84)
Education†		
<12 years	233 (45)	186 (36)
12 years	137 (27)	186 (36)
>12 years	147 (28)	146 (28)
Occupation‡		
Blue collar	172 (35)	194 (38)
White collar	192 (39)	175 (34)
Housewife	118 (24)	131 (26)
Unemployed	8 (2)	11 (2)
Smoking		
Never	235 (45)	247 (48)
Ever	283 (55)	271 (52)
Current	154 (30)	166 (32)
Past	129 (25)	105 (20)

* Nine cases and 29 controls did not report marital status.

† One case did not report years of education.

‡ Twenty-eight cases and seven controls did not report occupation.

and in combination for sex, age, race, smoking, parental smoking, education, and occupation does not change this finding. Cancer risk from passive exposure to cigarette smoke appears greatest for females and for individuals who are not themselves smokers, with statistically significant risks limited to these subgroups. There are no apparent subgroup differences in risk with race or occupational category (blue collar or white collar), although risk appears greater for individuals with at least a high school education. Cancer risk in relationship to passive exposure to cigarette smoke also appears limited to individuals who are younger than age 50 years.

Cancer risks from passive smoking among smokers and nonsmokers are shown separately in table 4. Risk is clearly elevated among nonsmokers, with the twofold risk significant after adjustment for age, race, or sex. Risk is also elevated among smokers, but the 30 per cent increase in risk is only of borderline statistical significance. Among nonsmokers, risk does not differ with race, but the risk from passive exposure is statistically significant only among females and among individuals between the ages of 30 and 49 years, although it is also elevated for males. For smokers, risk is significantly elevated among females and whites. The twofold risk related to passive exposure among individuals younger than 30 years (table 3) is due to risk among individuals who are themselves smokers (OR = 2.3) (table 4). The lower risk among nonsmokers in this age group (OR = 1.4) contrasts with the greater risk among nonsmokers in the other age categories under age 50 years. This suggests that the cumulative exposure through passive means, alone, for this young group may be below that which would pose a risk.

For most cancer sites, the number of cases is too small for meaningful site-specific analysis. However, statistically significant risks in relationship to passive smoking are seen for breast cancer, cervical cancer, and endocrine cancers. Odds ratios adjusted for possible differences in the distributions of age and level of education are shown in table 5 for smokers and nonsmokers combined.

The twofold risk of breast cancer shown in table 5 is not substantially changed by adjustment for education, race, age, smoking status, or parental smoking. Breast cancer risk is greater among younger women (OR = 3.4 for women <50 years vs. OR = 1.1 for women ≥50 years) and those with at least a high school education (OR = 3.3 vs. OR = 1.0).

The twofold risk for cervical cancer

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TABLE 5

Overall cancer risk from smoking by spouse, adjusted separately† for potential confounding factors

Factor	% exposed‡		Crude OR†	Adjusted OR	95% CL† on adjusted OR
	Cases§ (n = 508)	Controls (n = 489)			
Crude risk	55	43	1.6**		(1.3, 2.1)
Sex					
Male	35	26	1.5**		
Female	65	51	1.6**	1.7**	(1.3, 2.2)
Age					
<30	39	24	2.0*		
30–39	55	39	1.9*	1.6**	(1.3, 2.1)
40–49	67	47	2.2**		
50+	56	54	1.2		
Race					
Nonwhite	50	34	1.6*		
White	58	45	1.7**	1.6**	(1.3, 2.1)
Smoking					
Nonsmokers	52	34	2.1**		
Smokers	58	51	1.3	1.6**	(1.3, 2.1)
Education					
<12 years	55	52	1.1		
12 years	61	35	2.9**	1.6**	(1.2, 2.1)
>12 years	50	41	1.5		
Occupation¶					
Blue collar	53	40	1.7*		
White collar	53	40	1.7*	1.7**	(1.2, 2.3)
Either parent smoked					
No	55	41	1.8**	1.8**	(1.3, 2.3)
Yes	57	44	1.7**		

* $p < 0.05$.

** $p < 0.01$.

† OR, odds ratio, after multiple adjustment for age, race, sex, education, and smoking status = 1.7, 95% confidence limits (CL) = (1.3, 2.3).

‡ Spouse ever smoked while married to study subject.

§ Numbers of cases are not equivalent to those shown in table 1 because of missing values for education or spouse smoking.

¶ Excludes housewives, those unemployed, and those missing data on occupation.

among individuals passively exposed to cigarette smoke is also not affected by adjustment for age, race, smoking status, or smoking by parents. The estimated risk is reduced somewhat by adjustment for level of education, but there is no clear pattern of risk with level of education. As for the other sites, risk appears greatest among younger women (OR = 2.9 for women <50 years vs. OR = 0.9 for women ≥50 years). Odds ratios are statistically significant for whites and for nonsmokers, but the magnitude of the risks for nonwhites and for smokers is similar.

There is also a statistically significant risk of endocrine tumors among exposed individuals, which remains after adjustment for potential confounding variables. In subgroup analyses, risk is significant for younger individuals, nonsmokers, individuals with a high school education, and individuals whose parents did not smoke.

Although the number of lung cancer cases is small (n = 22), lung cancer risk from passive exposure to cigarette smoking is examined in table 6 because of current interest in this site. The overall crude risk of 1.9 is not statistically significant. However, the odds ratios for females (OR = ∞) and for nonsmokers (OR = ∞) are statisti-

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TABLE 4

Overall cancer risk from passive exposure to cigarette smoke among smokers and nonsmokers, adjusted for potential confounding factors

Factor	Nonsmokers (n = 466)				Smokers (n = 532)			
	Cases†	Controls	Crude OR‡	Adjusted OR‡ (95% CL§)	Cases†	Controls	Crude OR‡	Adjusted OR‡ (95% CL§)
	No. (% exposed)	No. (% exposed)			No. (% exposed)	No. (% exposed)		
Crude risk	231 (52)	235 (34)	2.1**		278 (58)	254 (51)	1.3	
				(1.4, 3.0)				(0.9, 1.9)
Age								
<30	45 (22)	58 (17)	1.4		50 (54)	38 (34)	2.3	
30–39	36 (56)	49 (31)	2.8*	2.0**	51 (55)	48 (48)	1.3	1.4
40–49	63 (68)	48 (33)	4.3**	(1.4, 2.9)	67 (64)	66 (58)	1.3	(1.0, 1.9)
50+	87 (53)	80 (49)	1.2		110 (58)	102 (55)	1.1	
Sex								
Male	39 (13)	57 (9)	1.5	2.0**	128 (41)	102 (36)	1.2	1.5*
Female	192 (59)	178 (42)	2.0**	(1.3, 2.9)	150 (73)	152 (61)	1.7*	(1.0, 2.1)
Race								
Nonwhite	72 (53)	83 (31)	2.5**	2.0**	77 (47)	63 (48)	1.0	1.4
White	159 (51)	152 (36)	1.9**	(1.4, 3.0)	201 (63)	191 (52)	1.5*	(1.0, 1.9)

* $p < 0.05$.

** $p < 0.01$.

† Numbers of cases are not equivalent to those shown in table 1 because of missing values for spouse smoking.

‡ OR, odds ratio.

§ CL, confidence limits.

cally significant even though they are based on small numbers. Since only two lung cancer cases were nonsmokers and only seven were females, it is not possible to examine lung cancer in greater detail. Risk is also elevated among younger individuals and among those with at least a high school education.

Among nonsmokers alone, risks were significantly elevated for endocrine and cervical cancer, despite the loss of power from reducing the already small number of cases for site-specific analysis (table 7). The twofold risk for breast cancer seen overall is also seen for nonsmokers but is not quite statistically significant. Among smokers, the odds ratio is statistically significant for breast cancer only. However, the approximately twofold risk for cervical cancer is similar to that among nonsmokers.

There is no clear dose-response relationship for all cancer sites combined or for specific sites in relationship to either the number of years married to a smoker (adjusted for age) or the average number of cigarettes smoked per day. This is true for smokers and for nonsmokers and also when analysis is confined to those younger than age 50 years, to whom an effect of passive smoking appears limited.

DISCUSSION

We have found a significantly elevated overall cancer risk for individuals passively exposed to cigarette smoke. This cannot be readily explained by a number of other factors, including individual smoking habits and two measures of social class: education and broad occupational category. Elevated risks were seen for several specific cancer sites and were not limited to lung cancer or other "smoking-related" tumors. These findings might relate to other factors we have not measured or to deficiencies in study design. However, we have not been able to identify a possible confounder or a bias of selection or recall that could have caused the difference in smoking patterns of spouses between cases and controls. Study subjects and interviewers were told

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TABLE 5

Cancer risk from passive exposure to cigarette smoke, adjusted for age and education, all sites combined and specific sites

Site	Cases	Crude OR§	Adjusted OR§	95% CL‖ on adjusted OR§
	No.† (% exposed)‡			
All sites	508 (55)	1.6**	1.6**	(1.2, 2.1)
Lip, oral cavity, and pharynx	22 (55)	1.6	1.1	(0.4, 3.0)
Digestive system	39 (51)	1.4	1.0	(0.5, 2.2)
Respiratory system	32 (50)	1.3	1.0	(0.5, 2.4)
Lung	22 (59)	1.9	1.5	(0.6, 4.3)
Bone, connective tissue, and skin	42 (36)	0.7	0.7	(0.3, 1.5)
Breast¶	59 (69)	2.2**	1.8*	(1.0, 3.7)
Female genital system¶	170 (66)	1.9**	1.8**	(1.2, 2.8)
Cervix	101(67)	2.0**	1.8*	(1.1, 3.2)
Prostate¶	10 (30)	1.2	0.8	(0.1, 3.9)
Testis¶	5 (40)	1.9	2.6	(0.2, 49.9)
Urinary tract	6 (50)	1.3	1.1	(0.2, 7.6)
Eye, brain, and other nervous system	38 (32)	0.6	0.7	(0.3, 1.5)
Endocrine	26 (65)	2.5*	3.2**	(1.4, 9.4)
Hematopoietic	52 (44)	1.1	1.3	(0.7, 2.5)
Other	7 (57)	1.8	1.8	(0.3, 10.4)

* $p < 0.05$.

** $p < 0.01$.

† Numbers of cases are not equivalent to those shown in table 1 because of missing values for education or spouse smoking.

‡ For comparison, 210 of 489 controls (43%) were exposed.

§ OR, odds ratio.

‖ CL, confidence limits.

¶ Sex-specific comparison. Of 330 female controls, 51% were exposed. Of 159 male controls, 26% were exposed.

simply that the study was designed to look at smoking patterns in families.

Cases and controls were similar with regard to their own smoking histories. This was partly because of the choice of friend controls who tended to have similar smoking histories and because known smoking-related sites were underrepresented in the case population. Cases included in the study were generally younger than those with smoking-related tumors. Unavoidable delays between case identification and completion of interviews also contributed to the lack of smoking-related cancers. Persons with lung cancer and other smoking-related tumors were more likely to have died before they could be interviewed. In addition, because of the special interests of physicians at the hospital from which cases were identified, breast cancers and gynecologic cancers were overrepresented. As a result of this unintentional matching on smoking status, risks from passive smoking and direct smoking cannot be compared.

The route of exposure for the passive smoker is via inhalation. Reports of effects on upper respiratory tract function (2–6) are consistent with this. There has also been a report of mutagens measured in the urine of passive smokers (17), indicating that components of cigarette smoke enter the bloodstream and are circulated throughout the body of the passive smoker. Another report indicated that enzyme activity can be induced by passive exposure to cigarette smoke (18). These findings are tentative, but do suggest that an overall increase in cancer risk or an increase in risk for specific nonrespiratory sites following passive exposure to cigarette smoke is plausible.

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TABLE 6

Lung cancer risk from passive exposure to cigarette smoke, adjusted for potential confounding factors

Factor	Cases No. (% exposed)	Crude OR†	Adjusted OR†	95% CL‡ on adjusted OR†
Crude risk	22 (59)	1.9		(0.8, 5.0)
Sex				
Male	15 (40)	1.9		(1.1, 8.4)
Female	7 (100)	∞**	3.4*	
Smoking				
Nonsmokers	2 (100)	∞*		
Smokers	20 (55)	1.2	1.5	(0.6, 3.9)
Age				
<50	5 (80)	6.7		
50+	17 (53)	1.0	1.5	(0.6, 3.8)
Education				
<12 years	15 (47)	0.8		
12 years	4 (100)	∞**	1.6	(0.6, 4.4)
>12 years	3 (67)	2.8		
Either parent smoked§				
No	6 (50)	1.5	1.5	(0.5, 4.8)
Yes	9 (56)	1.6		

* $p < 0.05$.
** $p < 0.01$.
† OR, odds ratio.
‡ CL, confidence limits.
§ Numbers reduced because of missing data on parental smoking.

TABLE 7

Cancer risk from passive exposure to cigarette smoke among smokers and nonsmokers: selected sites

Site	Nonsmokers			Smokers		
	No. of cases	Odds ratio	(95% CL†)	No. of cases	Odds ratio	(95% CL†)
Lung	2	∞‡		20	1.2	(0.5, 2.9)
Breast	32	2.0	(0.9, 4.3)	27	2.8*	(1.0, 7.6)
Cervix	56	2.1*	(1.2, 3.9)	45	2.0	(0.9, 4.1)
Endocrine glands	13	4.4*	(1.2, 17.4)	13	1.5	(0.4, 5.5)

* $p < 0.05$.
† CL, confidence limits.
‡ $p = 0.051$.

Our study was intended to consider a range of effects similar to what might be measured in a prospective study of a cohort of individuals who are passively exposed. Such an approach serves to single out sites which appear to be important as well as to investigate whether passive exposure might increase susceptibility to additional insults, thereby increasing cancer risk overall. Two reports in the literature use prospectively collected data (9, 11). One of these (11), however, does not provide data on cancer risks at sites other than the lung, and neither report provides data on overall cancer risk from passive exposure to cigarette smoke. Data from the Japanese study recently presented by Hirayama, however, indicate that cancer risk may be increased at sites other than the lung and that risk may not be limited to smoking-related sites (Hirayama, personal communication: presented at Hawaii Cancer Conference, 1984).

For this study, passive exposure during adult life is determined from a question-

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naire report of the number of years of married life during which a spouse smoked. Misclassification of exposure status is likely for individuals who never married but have lived with other persons who smoked. Slightly more controls than cases reported never marrying, which might lead to differential misclassification. However, we reanalyzed our data, excluding subjects who never married, and found the results to be the same. When only married subjects were included, the odds ratio for cancers of all sites combined was also 1.6. We made no allowances for multiple spouses, other members of the household who smoke, or passive exposures which occur outside of the home. Quantity smoked, too, is an approximate measure. The reported number of cigarettes smoked per day by the spouse is simply the average daily amount smoked during that time period. No allowance was made for changes in smoking habits of the spouse over time or for time since last exposure if the spouse did not smoke during the entire married interval.

Nonetheless, we found smoking by spouse to be significantly associated with overall cancer risk. The odds ratio of 1.6 was not substantially altered by adjustment for age, race, sex, smoking status, education, or occupation. Risk was limited to individuals younger than age 50 years, who were at approximately twofold risk. Risk was also greatest for females and nonsmokers, although not entirely limited to these groups.

When smokers and nonsmokers are considered separately, the twofold risk among nonsmokers is highly significant and is not altered by adjustment for potential confounding factors. The 30 per cent increase in risk among smokers whose spouses also smoke is only of borderline statistical significance, but is also unchanged by adjustment for other factors. The groups for whom risk from passive smoking appeared greatest are those groups generally at lower cancer risk overall. It may be that the small risk imposed by passive exposure during adult life is difficult to detect statistically in individuals at risk from other causes. Also, women who smoke may tend to smoke less, start later, and inhale differently than men. This would allow for a greater impact of passive exposure among women, regardless of their own smoking status. In addition, very few nonsmoking men are married to smokers, making it more difficult to detect a risk among males. In our data, only 10 per cent (10/96) of nonsmoking males were married to smokers, whereas 51 per cent (189/370) of nonsmoking females were married to smokers.

The increased cancer risk from passive exposure was not limited to sites generally thought to be smoking-related (12, 13). In fact, because of our case selection procedures and delays in interviewing cancer cases, individuals with cancers of smoking-related sites were only a small proportion of total cases. If cancers of the esophagus, respiratory tract, oral cavity and pharynx, urinary tract, and pancreas are designated smoking-related, the odds ratio for smoking-related tumors is 1.3, whereas the odds ratio for other sites is 1.7 ($p < 0.01$). Evidence is accumulating that cancer of the cervix should also be included among those sites that are smoking-related (19–21). When the cervix is included, the odds ratio for smoking-related sites is 2.0 and for other sites is 1.5, both of which are statistically significant.

Only 22 lung cancer cases are included in this report, with an odds ratio of 1.9 among passive smokers. Although not statistically significant, it is consistent with the level of risk reported in other studies. For women and for nonsmokers, the risk of lung cancer among those passively exposed was significantly increased despite very small numbers. The odds ratio for individuals under age 50 years was of borderline significance. Hirayama (9) reported a twofold risk for women married to smokers and found that risks were also greatest among younger women (as measured by husband's age). While Garfinkel (11) didn't find ar

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overall relationship of passive exposure to lung cancer risk, the relative risk among women married to smokers was in the same direction. Relatively few women in Garfinkel's cohort were under age 50 years, which might explain these inconsistent results.

In a study reported by Correa et al. (10), a twofold relative risk was seen among nonsmokers married to smokers. The risks were similar for males and females, although the number of nonsmoking males with lung cancer was very small. Among smokers, males who were light smokers with wives who were heavy smokers had a relative risk of 1.5. Trichopoulos et al. (7, 8) also reported an overall twofold lung cancer risk which was statistically significant among nonsmoking women married to smokers.

The studies reported by Trichopoulos et al. (7, 8), Correa et al. (10), and Hirayama (9) all suggest a dose-response relationship, although different measures of dose were employed in the three studies. In our study, there was no apparent dose-response using either years married to a smoker or average amount smoked by spouse as the measure of dose, but the number of lung cancer cases may be too small to expect a consistent trend. Evaluation of dose is not straightforward and depends on factors which we did not measure, such as room ventilation and smoking "style" of the spouse.

We found a twofold cervical cancer risk, which persisted after adjustment for level of education, among women whose husbands smoked. We did not collect data on sexual activity of cases or spouses. We also see an increased risk of breast cancer. Since the sociodemographic risk factors for these two sites are not the same, this supports the conclusion that the apparent excess cervical cancer risk is not entirely due to confounding by social class. Buckley et al. (22) reported a fourfold risk of cervical cancer among women whose husbands smoked, but after adjustment for number of sexual partners of the husband, the resulting twofold relative risk was not significant. Similar results were reported by Brown et al. (23). Hirayama (9) did not find elevated cervical cancer risk among women whose husbands smoked. This may relate to differences in the ages of the women studied or to differences in risk from other factors.

No previous study has reported a positive association between breast cancer and either passive or direct exposure to cigarette smoke (24–26). In a recently reported study by Rosenberg et al. (27), the relative risk for breast cancer was approximately 1.0 for exsmokers, current smokers, and heavy smokers as compared with nonsmokers. The crude odds ratio of 2.2 that we report is not reduced by adjustment for a number of potential confounding variables. Risk is not seen among women older than age 50 years or among women with less than a high school education, but is fairly constant across all other groups. Petrakis (28) has detected nicotine in breast fluid of nonlactating women who smoked, which may lead to alterations in breast tissue. This would support a possible role for passive smoking if passive exposure also caused such an effect.

One other site for which we find an association with passive exposure, endocrine glands, is not generally thought to be smoking-related. The number of tumors here is small, of which 11 are thyroid tumors.

In summary, passive exposure to smoking by spouse is related to an overall risk of cancer in our data. This association persists after adjusting for possible confounding factors. Associations with several specific tumor sites are also statistically significant, including some which are not ordinarily regarded as smoking-related. Further studies are required to confirm this broad spectrum of carcinogenicity by passive smoking and to explore the unexpected site-specific findings.

References

1. Harlap S, Davies AM. Infant admissions to hospital and maternal smoking. Lancet 1974;1:529-32.
2. Tager IB, Weiss ST, Munoz A, et al. Longitudinal

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study of the effects of maternal smoking on pulmonary function in children. N Engl J Med 1983;309:699-703.
3. Cameron P, Kostin JS, Zaks JM, et al. The health of smokers' and nonsmokers' children. J Allergy 1969;43:336-41.
4. Norman-Taylor N, Dickinson VA. Dangers for children in smoking families. Community Med 1977;128:32-3.
5. Cameron P, Robertson D. Effect of home environment tobacco smoke on family health. J Appl Psychol 1973;57:142-7.
6. White JR, Froeb HF. Small airways dysfunction in non-smokers chronically exposed to tobacco smoke. N Engl J Med 1980;302:720-3.
7. Trichopoulos D, Kalandidi A, Sparros L, et al. Lung cancer and passive smoking. Int J Cancer 1981;27:1-4.
8. Trichopoulos D, Kalandidi A, Sparros L. Lung cancer and passive smoking: conclusion of Greek study. Lancet 1983;2:677-8.
9. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 1981;282:183-5.
10. Correa P, Pickle LW, Fontham E, et al. Passive smoking and lung cancer. Lancet 1983;2:595-7.
11. Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. JNCI 1981;66:1061-6.
12. United States Department of Health and Human Services. Smoking and health: a report of the Surgeon General. DHHS publication no. (PHS) 79-50066.
13. United States Department of Health and Human Services. The health consequences of smoking—cancer: a report of the Surgeon General. DHHS publication no. (PHS) 82-50179.
14. Wynder EL, Goodman MT. Smoking and lung cancer: some unresolved issues. Epidemiol Rev 1983;5:177-207.
15. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies. JNCI 1959;22:719-48.
16. Gart JJ. Point and interval estimation of the common odds ratio in the combination of 2×2 tables with fixed marginals. Biometrika 1970;57:471-5.
17. Bos RP, Theuws JLG, Henderson PT. Excretion of mutagen in human urine after passive smoking. Cancer Lett 1983;19:85-90.
18. Manchester DK, Jacoby EH. Sensitivity of human placental monooxygenase activity to maternal smoking. Clin Pharmacol Ther 1981;30:687-92.
19. Marshall JR, Graham S, Byers T, et al. Diet and smoking in the epidemiology of cancer of the cervix. JNCI 1983;70:847-51.
20. Trevathan E, Layde P, Webster LA, et al. Cigarette smoking and dysplasia and carcinoma in situ of the uterine cervix. JAMA 1983;250:499-502.
21. Lyon JL, Gardner JW, West DW. Smoking and carcinoma in situ of the uterine cervix. Am J Public Health 1983;73:558-62.
22. Buckley JD, Harris RWC, Doll R, et al. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981;2:1010-15.
23. Brown DC, Pereira L, Garner JB. Cancer of the cervix and the smoking husband. Can Fam Physician 1982;28:499-502.
24. Vessey MP, Doll R, Jones K, et al. An epidemiological study of oral contraceptives and breast cancer. Br Med J 1979;1:1757-60.
25. Doll R, Gray R, Haffner B, et al. Mortality in relation to smoking: 22 years' observations on female British doctors. Br Med J 1980;280:967-71.
26. Porter JB, Jick H. Breast cancer and cigarette smoking (letter). N Engl J Med 1983;309:186.
27. Rosenberg L, Schwingl PJ, Kaufman DW, et al. Breast cancer and cigarette smoking. N Engl J Med 1984;310:92-4.
28. Petrakis NL. Nicotine in breast fluid of nonlactating women. Science 1978;199:303-5.
29. Sandler DP, Everson RB, Wilcox AJ, et al. Cancer risk in adulthood from early life exposure to parent's smoking. Am J Public Health, in press.

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Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer

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Personal cigarette smoking and exposure to passive smoke as risk factors for cervical cancer were examined in a population-based, case-control study conducted in Utah. Personal cigarette smoking was found to increase the risk of cervical cancer, after adjusting for age, educational level, church attendance, and sexual activity. The adjusted risk estimate associated with being a current smoker was 3.42 (95% confidence interval [CI], 2.10 to 5.57); for having smoked for 5 or more pack-years, it was 2.81 (95% CI, 1.73 to 4.55); and for having smoked at least 100 lifetime cigarettes, it was 2.21 (95% CI, 1.44 to 3.39). The adjusted risk estimate (also adjusted for actual cigarettes smoked) associated with passive smoke exposure for 3 or more hours per day was 2.96 (95% CI, 1.25 to 7.03). Risk from passive smoking was greater in women who were not smokers (odds ratio, 3.43; 95% CI, 1.23 to 9.54) than in women who smoked (odds ratio, 2.59; 95% CI, 0.23 to 29.24).

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IN 1977, Winkelstein[1] hypothesized that cigarette smoking was related to cervical cancer. This hypothesis was based on the observation that cigarette smoking is most strongly associated with squamous cell carcinomas, such as those of the lung and larynx. Squamous cell carcinomas are also the most preponderant histological type among cancers of the cervix uteri. Since 1977, this hypothesis has been expanded[2] and several studies have provided supportive data.[3-6] Passive smoking is the inhalation of smoke from tobacco products used by others. Studies have shown passive smoking to increase the risk of lung cancer,[7-11] although the risk associated with passive smoking and other squamous cell carcinomas has not been studied.

For editorial comment see p 1631.

The purpose of this study was to examine the cervical cancer risk associated with actual cigarette smoking and exposure to passive smoke. Because a large percentage of the population in Utah are members of the Church of Jesus Christ of Latter-day Saints (Mormons), which proscribes the use of tobacco, we were able to examine risk from exposure to passive smoke in nonsmokers as well as in smokers.

METHODS

A population-based, case-control study was conducted in the urban areas of Utah between 1984 and 1987. Women who were residing in Salt Lake, Davis, Weber, and Utah counties (the Wasatch Front) and who were between the ages of 20 and 59 years were eligible for inclusion in the study. This study was restricted to white women because less than 5% of the Utah population is nonwhite.

Study Population

A rapid reporting system was used to identify cases of cervical cancer within 6 weeks of diagnosis. Using this system, all 15 pathology laboratories along the Wasatch Front were visited monthly, and histological slides for cases of severe dysplasia, carcinoma in situ (CIS), and invasive squamous cell carcinoma of the cervix uteri were retrieved. A single study pathologist reviewed all slides in a blind manner and made the final determination of disease classification and eligibility for inclusion in the study. Based on the diagnosis of the study pathologist, women who had a first, primary cancer diagnosis of in situ or invasive squamous cell carcinoma of the cervix (International Classification of Diseases oncology code 180) were included in the study. The Utah Cancer Registry was used to verify complete case ascertainment. Histological material for women identified through the Utah Cancer Registry was also reviewed by the study pathologist. From a total of 350 women with CIS and 60 women with invasive carcinoma, 234 women (67%) with CIS and 36 women (60%) with invasive carcinoma were interviewed (66%). Four cases were excluded because of missing or unreliable data.

Controls were selected to categorically match cases in 5-year age intervals and by the county of residence using a random-digit–dialing telephone sam-

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pling technique.[12] Of the 635 controls identified, 480 (76%) agreed to be interviewed. Women who had a hysterectomy prior to 1984 were excluded, and 6 additional controls were excluded because of missing or unreliable data. A more detailed description of study completion rates is presented elsewhere.[13]

Data Collection

Personal interviews were conducted in the respondents' homes by trained interviewers and lasted approximately 1½ to 2 hours. Information obtained included (1) demographic data such as age, marital status, religious preference, church attendance practices, education, and income; (2) detailed dietary intake data; (3) lifetime cigarette usage; (4) the level of exposure to passive smoke; (5) a limited medical history; (6) use of contraceptives; and (7) a self-administered sexual history questionnaire. Additionally, women were asked to voluntarily give 20 mL of blood so that the presence or absence of antibodies to herpes simplex virus could be ascertained. Serum cotinine levels were determined by the method described by Haley et al[14] to validate self-reported smoking practices. Five hundred forty-two women (80% of cases and 81% of controls) agreed to have their blood drawn.

Cigarette-use questions included whether they had ever smoked 100 or more cigarettes in their lifetime, the age of smoking initiation, if they smoked continuously from the time they started, their inhalation practices, the number of years they had smoked, and the average number of cigarettes smoked per day. The last two variables were used to calculate the pack-year smoking history for each woman. It was also ascertained if the women had smoked cigarettes during the past 3 days, so that recent cigarette smoking practices could be compared with the results of the serum cotinine assays.

Several questions were asked about exposure to passive smoke. These questions had been pilot tested in a previous case-control study of similarly aged women and modified based on their responses. Women were asked if during the past 5 years they were exposed to "a lot, some, a little, or none at all" of smoking by others both inside and away from their homes. These categories were based on the methodology developed by Jarvis et al[15] to quantify passive smoking exposure. Additionally, women were asked to give an estimate of the number of hours per day, week, or month they were exposed to cigarette smoke both inside and away from their homes for the past 5 years. The period of 5 years prior to interview was chosen to be consistent with methods used by others[16] and to provide a reference period prior to disease.

Table 1.—Characteristics of Study Population

Characteristics	No. (%) of Women	
	Cases (n = 256)	Controls (n = 408)
Carcinoma in situ	231 (87)	
Invasive carcinoma	35 (13)	
Age, y		
20-29	92 (35)	143 (35)
30-39	123 (46)	159 (39)
40-49	37 (14)	71 (17)
50-59	14 (5)	35 (9)
Education		
<High school	135 (51)	100 (25)
High school	115 (43)	252 (62)
>High school	16 (6)	56 (14)
Religion		
LDS*	113 (42)	267 (65)
Non-LDS	153 (58)	141 (35)
Church attendance		
<1/mo	191 (72)	132 (32)
1-3/mo	26 (10)	38 (9)
≥1/wk	49 (18)	238 (58)
No. of sexual partners of woman†		
≤1	25 (10)	210 (52)
2-3	54 (21)	73 (18)
4-5	47 (19)	53 (13)
6-10	57 (23)	39 (10)
>10	69 (27)	28 (7)

*LDS indicates members of the Church of Jesus Christ of Latter-day Saints
†Some women did not complete the confidential questionnaire that contained sexual history.

Data Analyses

Results from the crude analyses were similar for CIS and invasive cervical cancer cases, and, thus, the results presented herein include all CIS and invasive cases combined and compared with controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the risk of cervical cancer associated with cigarette smoking and exposure to passive smoke. Stratified analyses were used to identify potential confounding variables. Socioeconomic status, as reflected by education and income; sexual activity; and frequency of church attendance were found to be confounding variables in this study and have been reported as risk factors for cervical cancer by others.[16-18] These variables were further tested in multiple logistic analyses to determine which variables resulted in the best-fitting logistic model. Multiple logistic regression models were used to remove the confounding effects of these associated variables on the smoking and cervical cancer relation and to determine if significant linear associations existed.[19]

It is difficult to offer a biologic explanation for the relationship of church attendance and educational level (as an indicator of socioeconomic status) to cervical cancer risk; however, both of these variables were controlled for in the final multiple logistic regression models because we believe they are proxies for some unidentified confounding variables. Age was also controlled in the final models, because slight confounding was present from this variable. Sexual activity was found to be the major confounding variable in this study, as it had the greatest effect on the risk estimates for smoking as well as contributed the most to the fit of the logistic models. The risk associated with passive smoking was assessed separately in smokers and nonsmokers. Interaction between passive smoking and actual cigarette smoking was also assessed by both multiplicative and additive models as described by Rothman.[20]

RESULTS

The characteristics of the study population are given in Table 1. Eighty-seven percent of the cases had CIS and 13% had invasive carcinomas. Cases tended to have lower levels of education and income (income not shown) and a greater number of sexual partners than did controls. Controls more frequently reported being members of the Church of Jesus Christ of Latter-day Saints and attending church at least once per week. Church attendance was a proxy measure for adherence to the church teachings.

To validate cigarette smoking prac-

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Table 2.—Comparison of Reported Cigarette Smoking During the 3 Days Prior to Interview and Measurement of Serum Cotinine Levels

Smoking Status	Cotinine Level		
	None Detected	1-15 ng/mL	>15 ng/mL
Cases (n = 212)			
Reported nonsmoker	90	3	4
Reported smoker	1	2	112
Controls (n = 330)			
Reported nonsmoker	285	3	4
Reported smoker	1	0	37

Table 3.—Cervical Cancer Risk Associated With Cigarette Smoking

Cigarette Smoking	No. of Cases	No. of Controls	Odds Ratio (95% Confidence Interval)*	
			Crude	Adjusted
Smoking status				
Never	81	305	1.00†	1.00†
Ex-smoker	37	48	2.90 (1.79-4.70)	1.41 (0.82-2.45)
Current smoker	148	55	10.13 (7.00-14.67)	3.42 (2.10-5.57)
Cigarette smoker				
<100 Cigarettes	81	305	1.00†	1.00†
≥100 Cigarettes	185	103	6.76 (4.86-9.41)	2.21 (1.44-3.39)
No. of cigarettes/d				
None	81	305	1.00†	1.00†
1-15	84	51	6.20 (4.14-9.29)	2.23 (1.34-3.69)
>15	101	52	7.31 (4.94-10.82)	2.19 (1.33-3.62)
No. of years smoked				
None	81	305	1.00†	1.00†
0.001-10	75	42	6.72 (4.40-10.27)	1.68 (1.01-2.80)
>10	110	81	6.79 (4.85-9.91)	2.17 (1.20-3.90)
Pack-years				
None	81	305	1.00†	1.00†
0.05-5	47	29	6.10 (3.75-9.94)	1.50 (0.87-2.59)
>5	138	74	7.02 (4.91-10.03)	2.81 (1.73-4.55)
Continuous smoker				
Never smoked	81	305	1.00†	1.00†
Start and stop	81	58	5.25 (3.53-7.84)	1.61 (0.97-2.67)
Continuous	104	45	8.70 (5.84-12.92)	3.00 (1.80-4.99)
Inhale				
Nonsmoker	81	305	1.00†	1.00†
Mouth/throat	25	9	10.46 (5.29-20.67)	3.32 (1.38-7.97)
Chest	159	92	6.50 (4.63-9.15)	2.34 (1.52-3.61)
Age first smoked, y				
Never	81	305	1.00†	1.00†
>16	86	55	5.88 (3.85-8.77)	2.43 (1.38-3.70)
≤16	99	48	7.78 (5.22-11.58)	2.58 (1.54-4.31)

*Odds ratios and 95% confidence intervals were calculated from multiple logistic regression analyses and adjusted for age, church attendance, education, and number of sexual partners of the woman.
†All values compared with the lowest level.

tices, we compared reported cigarette smoking during the 3 days prior to the interview with serum cotinine levels. Women were divided into 3 groups, those who had no detectable levels of serum cotinine, those who had low levels of serum cotinine, and those who had serum cotinine levels above 15 ng/mL (Table 2). In most instances, low levels of cotinine may not represent actual cigarette smoking, but may indicate exposure to passive smoke. While we did not observe serum cotinine levels to be sensitive to reported exposure to passive smoke, others have reported serum cotinine levels for exposure to passive smoke between 0.5% and 6.0% of the mean reported for cigarette smokers.[11] Therefore, we have used a cut-off point for serum cotinine of 15 ng/mL to assess the validity of reported smoking practices.

Of women who reported not smoking, only 4 cases and 4 controls had levels of serum cotinine above 15 ng/mL, and only 2 cases and 1 control had levels above 50 ng/mL. We have also compared women who reported smoking 3 days prior to the interview and those who also reported having smoked 100 or more cigarettes during their lifetime. We found that none of the women who reported smoking fewer than 100 cigarettes in their lifetime reported smoking during the 3 days prior to interview; however, 99 women said they did not smoke during the past 3 days, although they had smoked at least 100 cigarettes during their lifetime. Because of the excellent agreement between reported cigarette smoking practices and serum cotinine levels and because all of the respondents reported cigarette use history, the reported cigarette history is used in these analyses.

Personal Smoking Risk

Assessment of cervical cancer risk associated with cigarette smoking practices is shown in Table 3. More than half of the cases (148 [56%]) reported cigarette smoking while most of the controls (305 [75%]) reported never smoking cigarettes. Risk estimates associated with smoking were greatly attenuated by sexual history, reflected by the number of sexual partners of the woman. All cigarette smoking practices gave similar estimates of risk, with an adjusted risk for current smokers of 3.42 (95% CI, 2.10 to 5.57); for smoking 100 or more cigarettes during the lifetime it was 2.21 (95% CI, 1.44 to 3.39); for smoking more than 15 cigarettes per day it was 2.19 (95% CI, 1.33 to 3.62; $P = .001$, for linear trend). The risk associated with smoking for 5 pack-years was 2.81 (95% CI, 1.73 to 4.55; $P = .0035$, for linear trend), and for smoking for more than 10 years it was 2.17 (95% CI, 1.20 to 3.90; $P = .0029$, for linear trend). Women who first started to smoke when they were 16 years of age or younger had an adjusted risk estimate of 2.58 (95% CI, 1.54 to 4.31). Likewise, women were at a greater risk if they smoked continuously (adjusted OR, 3.00; 95% CI, 1.80 to 4.99) than if they started and stopped (adjusted OR, 1.61; 95% CI, 0.97 to 2.67).

We further explored the effects of having smoked 100 or more cigarettes ("ever smoked") vs never having smoked 100 cigarettes for different age and sexual activity groups (Table 4). Cigarette smoking was a greater risk factor for cervical cancer in women under 30 years of age than in women older than 30 years, with an OR of 6.81 (95% CI, 3.28 to 14.14) being observed for ever having smoked. Women who smoked but had one or fewer sexual partners experienced the greatest risk from cigarette smoking, with an OR of 14.19 (95% CI, 9.17 to 38.92) being observed. This finding could reflect the fact that cigarette smoking is a more important risk factor in women who have not experienced other major risk factors.

Passive Smoking Risk

Exposure to passive smoke was an independent risk factor for cervical can-

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cer (Table 5). The risk estimate associated with an exposure to passive smoke for 3 or more hours a day was 2.96 (95% CI, 1.25 to 7.03; $P = .0028$, for linear trend), after adjusting for age, years of education, church attendance, number of sexual partners, and pack-years of cigarettes smoked (Table 5). (Analyses were also done that controlled for the number of sexual partners of the mate; however, because approximately 100 women did not report the sexual history of their current mate and because results were similar to those observed when controlling for the number of sexual partners of the women, the results presented are adjusted for number of sexual partners of the woman.)

Exposure to passive smoke in the home was a greater risk factor than exposure to passive smoke away from the home. The OR associated with exposure to greater than 1.5 hours per day of passive smoke in the home was 2.29 (95% CI, 1.39 to 3.77; $P = .0041$, for linear trend); while the risk associated with smoke away from home was 1.48 (95% CI, 0.74 to 2.95; $P = .0781$, for linear trend). Similar estimates of risk were seen when women reported the actual number of hours of exposure to passive smoke as when they reported exposure as "none, a little, some, or a lot." Again, exposure to a lot of passive smoke in the home resulted in a twofold increased risk of developing cervical cancer. Analyses of risk associated with passive smoking by age and sexual activity groups showed that women who were 40 years or older were at a greater risk from exposure to passive smoking after controlling for number of sexual partners and actual smoking (OR, 11.71; 95% CI, 2.24 to 61.24) than were women younger than 40 years. No differences in risk by the number of sexual partners of the woman were observed, with the highest level of passive smoke exposure resulting in a twofold to threefold increased risk in all groups.

Because risk associated with exposure to passive smoke may be different in smokers and nonsmokers, we stratified for smoking status and assessed the risk of passive smoking in these two groups (Table 6). Exposure to 3 or more hours of passive smoke in nonsmokers resulted in an increased risk of 3.43 (95% CI, 1.23 to 9.54; $P = .0179$, for linear trend). The risk was less when we looked at the lower levels of exposure (0.01 to 1.5 h/d) either in the home or away from the home (OR, 2.66 and 2.30, respectively; $P = .0362$ and $P = .0994$, for linear trend, respectively). Because few smokers were not exposed to passive smoke, it was more difficult to assess the risk of passive smoking in smokers. Although, there was insufficient power in our study to detect a statistically significant difference between levels of exposure, increasing levels of exposure resulted in an increasing risk for cervical cancer, with smokers exposed to 3 or more hours of passive smoke per day having an increased risk of 2.59 (95% CI, 0.23 to 29.24; $P = .1298$, for linear trend). Further analyses of interaction, by the methods described by Rothman[28] between passive smoking and actual cigarette smoking, showed interaction between these two variables.

Table 4.—Cervical Cancer Risk Associated With Cigarette Smoking by Age and Number of Sexual Partners

Characteristics	No. of Cases		No. of Controls		Adjusted Odds Ratio* (95% Confidence Interval)
	Non-smokers	Smokers	Non-smokers	Smokers	
Age, y					
20-29	18	74	110	33	6.81 (3.26-14.14)
30-39	43	80	117	42	3.04 (1.72-5.37)
40-59	20	31	78	28	2.30 (1.02-5.33)
No. of sexual partners of woman					
0-1	13	12	197	13	14.19 (5.17-38.92)
2-3	19	35	51	22	4.51 (2.08-9.79)
≥4	46	127	54	66	2.34 (1.42-3.87)

*Compares smokers relative to nonsmokers within various strata of age and number of sexual partners. Odds ratios for age were also adjusted for number of sexual partners, odds ratios for number of sexual partners were also adjusted for age.

Table 5.—Cervical Cancer Risk Associated With Exposure to Passive Smoke

Exposure	No. of Cases	No. of Controls	Odds Ratio (95% Confidence Interval)	
			Crude	Adjusted*
Passive smoke, h/d				
None	9	78	1.00†	1.00†
0.1-0.9	53	169	2.71 (1.30-5.67)	1.20 (0.52-2.76)
1.0-2.9	43	64	5.68 (2.70-11.97)	1.60 (0.65-3.96)
≥3.0	161	94	14.84 (7.96-27.67)	2.96 (1.25-7.03)
In-home passive smoke, h/d				
None	80	278	1.00†	1.00†
0.1-1.5	52	63	2.86 (1.86-4.43)	0.97 (0.56-1.68)
>1.5	134	66	7.05 (4.86-10.20)	2.29 (1.39-3.77)
Away-from-home passive smoke, h/d				
None	22	88	1.00†	1.00†
0.1-1.5	130	234	2.22 (1.34-3.69)	1.07 (0.57-2.00)
>1.5	114	84	5.42 (3.22-9.15)	1.48 (0.74-2.95)
In-home passive smoke				
None	80	277	1.00†	1.00†
Little	32	44	2.51 (1.51-4.19)	0.94 (0.51-1.73)
Some	57	40	4.93 (3.14-7.76)	1.81 (1.02-3.24)
A lot	97	45	7.46 (4.96-11.22)	2.04 (1.18-3.51)
Away-from-home passive smoke				
None	22	87	1.00†	1.00†
Little	54	104	2.05 (1.18-3.62)	1.06 (0.54-2.17)
Some	99	150	2.61 (1.55-4.40)	1.02 (0.53-1.99)
A lot	91	66	5.45 (3.17-9.39)	1.38 (0.68-2.81)

*Odds ratios and 95% confidence intervals are adjusted for age, education, church attendance, number of sexual partners of the woman, and cigarette smoking.
†All values compared with the lowest level.

COMMENT

The results from this study support previous research that has shown that women who smoke cigarettes are at an increased risk of developing cervical cancer. The risk is greatest in women less than 30 years of age and in women who have had one or fewer sexual partners. This is probably because cigarette smoking will be a greater risk factor in women who do not have other major competing risk factors. The risk estimates for cigarette smoking observed by other investigators[24] are comparable with the adjusted OR of 2.2 observed in this study. Other studies[24] have shown risk estimates slightly lower than those we observed, which ranged from 1.5 to 1.8. A case-control study of 332 white women with cervical cancer and 1725 white controls by Stellman and colleagues[29] did not show cigarette smoking to be related to cervical cancer after adjusting for age and socioeconomic sta-

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Table 6.—Cervical Cancer Risk Associated With Exposure to Passive Smoke in Cigarette Nonsmokers and Smokers*

Exposure	Odds Ratio (95% Confidence Interval)	
	Nonsmokers†	Smokers‡
All passive smoke, h/d		
None	1.00§	1.00§
0.1-0.9	1.14 (0.45-2.94)	1.64 (0.14-19.31)
1.0-2.9	1.57 (0.52-4.73)	1.75 (0.15-20.03)
≥3.0	3.43 (1.23-9.54)	2.59 (0.23-29.24)
In-home passive smoke, h/d		
None	1.00§	1.00§
0.1-1.5	0.62 (0.25-1.53)	1.18 (0.54-2.53)
>1.5	2.66 (1.15-6.13)	1.89 (0.94-3.79)
Away-from-home passive smoke, h/d		
None	1.00§	1.00§
0.1-1.5	1.33 (0.58-3.07)	0.80 (0.25-2.63)
>1.5	2.30 (0.89-5.95)	0.73 (0.22-2.44)
In-home passive smoke		
None	1.00§	1.00§
Little	1.86 (0.37-9.37)	1.60 (0.59-4.34)
Some	1.49 (0.44-5.09)	2.47 (1.07-5.70)
A lot	2.93 (1.08-7.94)	1.26 (0.64-2.50)
Away-from-home passive smoke		
None	1.00§	1.00§
Little	1.58 (0.68-3.68)	0.87 (0.40-1.91)
Some	1.11 (0.49-2.50)	0.76 (0.38-1.52)
A lot	1.59 (0.57-4.45)	0.67 (0.32-1.40)

*Nonsmokers are defined as women who have smoked fewer than 100 cigarettes in their lives; smokers have smoked 100 or more cigarettes.

†Odds ratios and 95% confidence intervals were calculated from multiple logistic regression analyses and adjusted for age, education, church attendance, and number of sexual partners of the woman.

‡Also was adjusted for the number of cigarette pack-years.

§All values compared with the lowest level.

tus. A possible explanation for these conflicting results could be that the study by Stellman et al was not population based. Their cases were originally used as controls in another study, and their control group consisted of women hospitalized for nonneoplastic diseases. A study by West and colleagues[8] compared smoking and cervical cancer risks obtained from a population-based study with a hospital-based study and found that the risk for smoking and cervical cancer, as well as for several other risk factors, were lower in the hospital-based study because of the more "case-like" attributes of the control group.

We have shown that women who are exposed to the cigarette smoke of others are at an increased risk of cervical cancer. This increased risk is independent of the risks associated with personal cigarette smoking, educational level, church attendance, age, and number of sexual partners, although the greatest risk was in women who were nonsmokers. The risk associated with passive smoking in this study is as strong as that observed from personal cigarette smoking. While all smokers are exposed to their own smoke, few smokers reported not also being exposed to smoke by others. It is possible that there is more misclassification of passive smoking in smokers than in nonsmokers.

Few studies have looked at passive smoking and cervical cancer risk. Two studies[24,25] have looked at the husbands' smoking habits as a risk factor for cervical cancer. Hellberg et al[24] found that although smoking by the male partner was correlated with cervical cancer, this relationship disappeared when adjusting for the smoking habits of the woman. This study did not have sufficient sample size to assess the effect that the male partners who smoked had on nonsmoking cases. The study by Buckley et al[25] found a twofold increase in cervical cancer risk if the husband smoked. While they adjusted for sexual partners of the men, they did not adjust for smoking practices of the women.

The mechanisms whereby cigarette smoking may increase the risk of cervical cancer are beginning to be evaluated. Recent studies have shown that constituents from cigarette smoke can be transmitted through the blood to distant tissues and organs, and these substances have been detected in the uterine cervix of cigarette smokers.[26-28] Tobacco smoke is known to contain mutagens and carcinogens that may act as initiators and/or promoters in the uterine cervix, although no specific mutagens have been identified in cervical fluid.

Carcinogens in mainstream smoke (smoke inhaled from smoking) and sidestream smoke (smoke inhaled from being in areas where other people smoke) have been evaluated.[21,29,31] It has been shown that some substances, such as nitrosamines, occur in higher concentrations in side-stream smoke than in mainstream smoke.[9,29,32] Of interest in another analysis of our study population, the intake of vitamins C and E was found to be related to lower cervical cancer risk in smokers.[33] Both of these vitamins are known to be antagonists to nitrosamines.[34,35] Comparative estimates have been made regarding inhalation of passive smoke vs inhalation of substances while smoking. In 1 hour of passive smoking, it is estimated that particulate matter such as nicotine would be inhaled in one fourth to one fiftieth of that inhaled by smoking one cigarette,[29] while during the same amount of time, the exposure to nitrosamines is equivalent to smoking one-half pack of filtered cigarettes.[32]

We have also shown that personal cigarette smoking has an additive effect with passive smoke exposure. The combined risk of being a cigarette smoker and also being exposed to the tobacco smoke of others is greater than that observed for either risk factor separately. This finding needs to be verified in other studies designed to ascertain both passive and actual smoking and the cervical cancer risk.

In epidemiologic studies, determination of smoking status generally has relied on self-reported information. The validity of self-report data has been challenged, particularly in settings where the respondent perceived pressure to quit smoking, such as in smoking cessation programs.[37] An analogous situation is the proscription of the Church of Jesus Christ of Latter-day Saints against the use of tobacco products, which might lead some women to report their smoking practices inaccurately.

A strength of this investigation was the validation of reported smoking status with serum cotinine levels. The concentration of cotinine, regardless of whether from serum, saliva, or urine, has been demonstrated to be better than other smoking status tests.[38] Urinary cotinine levels are preferred as an indicator of passive smoking exposure.[39] The present findings support the inadequacy of serum cotinine for determination and quantification of passive smoke exposure since less than 2% of the study population fell within the 1- to 15-ng/mL range, whereas 47% reported some passive exposure in the home. We feel that this level of agreement is excellent, especially because the Church of Jesus Christ of Latter-day Saints proscribes the use of tobacco.

A second major strength of our inves-

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tigation was the population studied. Because a large segment of this population did not smoke cigarettes, we were able to assess passive smoking risk in nonsmokers as well as smokers. We evaluated several indicators of exposure to passive smoke and found that, regardless of the indicator used, the results were consistent. A third study strength is that a single study pathologist reviewed all the histological material of potential cases and made the final determination of eligibility so that we had consistent case definition. In addition to these other strengths, we have used community-based controls. We have also been able to assess the risk of cigarette smoking independently of sexual behavior. However, because of the strong association between sexual activity and cervical cancer risk and the strong association of sexual activity and smoking status, misclassification of sexual history could result in inflated risk estimates for smoking from uncontrolled confounding.

A limitation of our study was that only 66% of the cases and 76% of the potential controls completed the interview process. Completion rates of this magnitude are common in studies of cervical cancer where the population is often young, of low socioeconomic status, and highly mobile. Some studies have reported response rates of less than 50%.[40] We do not know the effects of nonresponse on our study results. Additionally, because only 35 cases of invasive cervical cancer had complete data for analysis, it was difficult to assess risk separately for invasive cancers. We did attempt to determine if cigarette smoking presented a greater risk for CIS than for invasive carcinomas. We did not see any differences and, therefore, combined the two groups for the final analyses. Others[41,42] have examined cigarette smoking in patients with CIS and invasive cervical cancer and likewise did not see differences in effect for these two categories of cervical cancer.

In summary, it seems that exposure to passive cigarette smoke and personal cigarette smoking are important in the etiology of cervical cancer. Exposure to passive cigarette smoke increases cervical cancer risk, especially in nonsmokers. The greatest risk associated with passive smoking is that inhaled in the home, possibly because people exposed to smoke at home incur larger doses of exposure either from being in a more confined area or having a more constant exposure. Further assessment of the effects of passive smoke on squamous cell carcinomas seems warranted. Additionally, studies that identify specific mutagens in cervical fluids of women exposed to large amounts of passive smoke would provide support for this observation.

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References

1. Winkelstein W. Smoking and cancer of the uterine cervix: hypothesis. *Am J Epidemiol*. 1977; 106:257-259.
2. Winkelstein W, Shillitoe EJ, Brand R, Johnson KK. Further comments on cancer of the uterine cervix, smoking, and herpesvirus infection. *Am J Epidemiol*. 1984;119:1-8.
3. Lyon JL, Gardner JW, West DW, Stanish WM, Hebertson RM. Smoking and carcinoma in situ of the uterine cervix. *Am J Public Health*. 1983;73:558-562.
4. Clarke EA, Morgan RW, Newman AM. Smoking as a risk factor in cancer of the cervix: additional evidence from a case-control study. *Am J Epidemiol*. 1982;115:59-66.
5. Trevathan E, Layde P, Webster LA, Adams JB, Benigno BB, Ory H. Cigarette smoking and dysplasia and carcinoma in situ of the uterine cervix. *JAMA*. 1983;250:499-502.
6. Vecchia CL, Franceschi S, Decarli A, Fasoli M, Gentile A, Tognoni G. Cigarette smoking and the risk of cervical neoplasia. *Am J Epidemiol*. 1986;123:22-29.
7. Brinton LA, Schairer C, Haenszel W, et al. Cigarette smoking and invasive cervical cancer. *JAMA*. 1986;255:3265-3269.
8. Marshall JR, Graham S, Byers T, Swanson M, Brasure J. Diet and smoking in the epidemiology of cancer of the cervix. *JNCI*. 1983;70:847-851.
9. Blot WJ, Fraumeni JF. Passive smoking and lung cancer. *JNCI*. 1986;77:993-1000.
10. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer*. 1981;27:1-4.
11. Pershagen G, Hrubec Z, Svensson C. Passive smoking and lung cancer in Swedish women. *Am J Epidemiol*. 1987;125:17-24.
12. Waksberg J. Sampling methods for random-digit dialing. *J Am Stat Assoc*. 1978;73:40-46.
13. Slattery ML, Abbott TM, Overall JC, et al. Dietary vitamins A, C, and E, and selenium as risk factors for cervical cancer. *Epidemiology*. In press.
14. Haley NJ, Axelrad CM, Tilton KA. Validation of self-reported smoking behavior: biochemical analyses of cotinine and thiocyanate. *Am J Public Health*. 1983;73:1204-1207.
15. Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Salloojee Y. Biochemical markers of smoke absorption and self-reported exposure to passive smoking. *J Epidemiol Community Health*. 1984;38:335-339.
16. Harris RWC, Brinton LA, Cowdell RH, et al. Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. *Br J Cancer*. 1980;42:359-369.
17. Hulka BS. Risk factors for cervical cancer. *J Chronic Dis*. 1982;35:3-11.
18. Brinton LA, Fraumeni JF. Epidemiology of uterine cervical cancer. *J Chronic Dis*. 1986; 39:1051-1065.
19. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Volume 1—The Analysis of Case-Control Studies*. Lyons, France: International Agency for Research on Cancer; 1980. IARC Scientific publication 32.
20. Rothman KJ. Interactions between causes. In: *Modern Epidemiology*. Boston, Mass: Little Brown & Co Inc; 1986.
21. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General*. Rockville, Md: US Dept of Health and Human Services; 1986.
22. Stellman SD, Austin H, Wynder EL. Cervix cancer and cigarette smoking: a case-control study. *Am J Epidemiol*. 1980;111:383-388.
23. West DW, Schuman KL, Lyon JL, Robison LM, Allred R. Differences in risk estimations from a hospital and a population-based case-control study. *Int J Epidemiol*. 1984;13:235-239.
24. Hellberg D, Valentin J, Nilsson S. Smoking and cervical intraepithelial neoplasia. *Acta Obstet Gynecol Scand*. 1986;65:625-631.
25. Buckley JD, Harris RWC, Doll R, Vessey MP, Williams PT. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet*. 1981;2:1010-1015.
26. Sasson IM, Haley NJ, Hoffman D, Wynder EL, Hellberg D, Nilsson S. Cigarette smoking and neoplasia of the uterine cervix: smoke constituents in cervical mucus. *N Engl J Med*. 1985;312:
27. Schiffman M, Brinton L, Holly E, et al. Regarding mutagenic mucus in the cervix of smokers. *JNCI*. 1987;78:590-591.
28. Schiffman MH, Haley NJ, Felton JS, et al. Biochemical epidemiology of cervical neoplasia: measuring cigarette smoke constituents in the cervix. *Cancer Res*. 1987;47:3886-3888.
29. Hellberg D, Nilsson S, Haley NJ, Hoffman D, Wynder E. Smoking and cervical intraepithelial neoplasia: nicotine and cotinine as serum and cervical mucus in smokers and nonsmokers. *Am J Obstet Gynecol*. 1988;158:910-913.
30. Strober W. Lung dynamics and uptake of smoke constituents by nonsmokers: a survey. *Prev Med*. 1984;13:589-601.
31. Triebig G, Zober MA. Indoor air pollution by smoke constituents: a survey. *Prev Med*. 1984; 13:570-581.
32. Brunnemann KD, Adams JD, Ho DPS, Hoffman D. The influence of tobacco smoke on indoor atmospheres, II: volatile and tobacco-specific nitrosamines in main and side stream smoke and their contribution to indoor pollution. In: *Proceedings of the Fourth Joint Conference on Sensing of Environmental Pollutants*. Washington, DC: American Chemical Society; 1978:876-880.
33. World Health Organization. Chemistry and analysis of tobacco smoke. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking*. Lyons, France: International Agency for Research in Cancer; 1985;38:83-128.
34. Ames BN. Dietary carcinogens and anticarcinogens. *Science*. 1983;221:1256-1264.
35. Watson RR, Leonard TK. Selenium and vitamins A, E, and C: nutrients with cancer prevention properties. *J Am Diet Assoc*. 1986;86:506-514.
36. Hugod C. Indoor air pollution with smoke constituents: an experimental investigation. *Prev Med*. 1984;13:582-588.
37. Allen P, Lundl B, Westling H. Carbon monoxide levels and reported cessation of smoking. *Psychopharmacology*. 1976;49:263-269.
38. Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Salloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. *Am J Public Health*. 1987;77:1435-1438.
39. Wall M, Johnson J, Jacob P, Benowitz N. Cotinine in the serum, saliva, and urine of nonsmokers, passive smokers and active smokers. *Am J Public Health*. 1988;78:699-701.
40. Fujimoto I, Nemoto H, Fukuda K, Masubuchi S, Masubuchi K. Epidemiologic study of carcinoma in situ of the cervix. *J Reprod Med*. 1985;30:535-540.
41. Terris M, Wilson F, Nelson JH. Comparative epidemiology of invasive carcinoma of the cervix, carcinoma in situ and cervical dysplasia. *Am J Epidemiol*. 1980;112:253-257.
42. Wigle DT, Mao Y, Grace M, RE. Smoking and cancer of the uterine cervix: hypothesis. *Am J Epidemiol*. 1980;111:125-127.

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Environmental Factors in the Etiology of Rhabdomyosarcoma in Childhood [1, 2, 3]

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ABSTRACT—In a case-control study of childhood rhabdomyosarcoma (RMS), families of 33 cases and 99 controls were interviewed. A relative risk (RR) of 3.9 was found associated with fathers' (but not mothers') cigarette smoking ($P=0.003$). Cases had had fewer immunizations than controls, particularly smallpox vaccination (RR=0.2; $P=0.001$), and conversely had more preventable infections. An RR of 3.2 ($P=0.03$) was found associated with exposure to chemicals and an RR of 3.7 ($P=0.004$) was found associated with diets that included organ meats. Mothers of cases were more likely to be over age 30 years at subject's birth, to have used antibiotics preceding or during pregnancy, and to have had an overdue and/or assisted delivery. Other findings suggest that low socioeconomic status is associated with an increased risk of RMS. These aggregate findings imply that environmental factors may play an important role in the etiology of childhood RMS.—JNCI 1982; 68:107-113.

RMS is the sixth most common cancer of childhood with an annual incidence of about 4 cases per million children (*1, 2*). Little is known about its epidemiologic features, and there are few etiologic hypotheses for this rare disease. Previous epidemiologic studies, based on mortality statistics and case series, indicate the following: Males are more susceptible than females, with whites being more susceptible than blacks; the peak incidence is at about ages 3-4 years; relatives of patients are at markedly increased risk of RMS; and there appears to be familial aggregation of RMS with other soft tissue sarcomas and breast cancer (*3-5*). In this first case-control study of childhood RMS we evaluated possible etiologic factors.

SUBJECTS AND METHODS

We attempted to identify all incident cases of childhood RMS in NC residents during the period 1967-76. Diagnostic indexes, tumor registries, and pathology logs were searched at 141 of the 150 nonpsychiatric hospitals in NC that admit children and at three major referral hospitals in two adjacent states. The nine nonparticipating institutions were military hospitals, which usually referred their pediatric oncology patients to in-state civilian hospitals for care. A total of 37 cases was identified, and the subjects were 0-14 years of age; all but 1 were diagnosed at an NC hospital. We also searched the NC State Tumor Registry and oncology records at the (then) three NC medical schools but found no additional cases. To be eligible for study, a patient ("case") had to have been born in NC and reside there at the time of a histopathologically confirmed diagnosis. Because birth certificates served as our means of selecting controls, cases also had to have a birth certificate on file with the NC Department of Human Resources. Four of the 37 cases were excluded: Two had been born out of state; 1 had been adopted (hence her birth certificate was not publicly listed), and another, although born in NC, had no birth certificate on file. For each of the 33 resulting cases, 3 controls of the same age (±2 mo), sex, and race were randomly selected from NC birth certificates. We excluded subjects who had been adopted, who had died during the neonatal period, or who had been born to parents serving in the military.

Recent addresses for case families were obtained in most instances from their physicians and from medical records. Current addresses for the parents of controls were obtained by a variety of means. The first resource was a library of telephone and city directories from which we tried to match an address with that on the birth certificate. Where necessary, we next searched driver's license and motor vehicle registries. In some instances it was possible to trace parents through the physician listed on the birth certificate. Our last resort was to visit the town of last known address and make inquiries of neighbors and at the post office.

Abbreviations used: NC=North Carolina; RMS=rhabdomyosarcoma; RR=relative risk(s); SES=socioeconomic status.

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[9] Recipient of a Preventive Cardiology Academic Award (K07HL-00633) from the National Heart, Lung, and Blood Institute.
[10] We thank the hospitals of North Carolina for their generous assistance; the Vital Records Branch of the North Carolina Department of Human Resources for providing us with controls; and Ms. M. Griffin, Ms. J. McMillan, Ms. J. Wood, and Ms. K. Baker for their long hours on North Carolina's highways and byways to interview our subjects.

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We were thus able to trace all 33 cases. Of the 99 controls first selected, only 70 were found and interviewed; 9 were located but refused to participate, and the other 20 were untraceable. These 29 controls were then replaced by children whose birth certificates were selected by the same methods described above. Twenty-three of these replacements were located and interviewed; 1 more was located but refused to participate, and the other 5 could not be found. A second replacement was chosen for these 6 controls by the same methods. Five of the 6 second-round replacements were interviewed, and 1 refused to cooperate. This control was replaced by a third-round selection.

Using the information on birth certificates, we assessed bias potentially introduced by our loss and replacement of original controls. First, we compared the participating original (first-round) controls with all of the lost and nonparticipating ones and found similar distributions of sex, race, date of birth, extent of parents' education, parents' age at birth of subject, region of residence, duration of pregnancy, and father's occupation (table 1). This finding indicates that the lost and nonparticipating controls were quite similar to the participating first-round controls. Second, we compared the lost and nonparticipating controls with their replacements. As shown in table 1, the only major difference between these 2 groups was in the area of father's occupation. Fewer replacement controls had fathers with professional or managerial occupations, and replacements had more prenatal visits.

Since our evaluation of potential bias was based on birth certificate information, we assessed the reliability of this information by checking it against our interview data. The correlation between fathers' occupations (in terms of "professional and managerial" vs. "other") from the two sources was 0.83. Similarly, the correlation coefficient for years of fathers' education was 0.58 and for years of mothers' education, 0.68.

After case and control families had been located, they were invited by letter to participate in a "study of child health." Interviews were then arranged by telephone call or home visit if the family had no telephone. A standard questionnaire was administered by trained interviewers. The mean duration of interviews for cases was 70.5 minutes and that for controls, 65.1 minutes. All but eight interviews were conducted in the subjects' homes. Three took place at the mothers' place of employment (1 case and 2 control mothers) and one at Duke University Medical Center (a case); four were done by telephone because the families had moved out of NC (2 cases and 2 controls). The informant in all but two instances was the subject's parent, usually the mother (91% of cases and 92% of controls).

In our analyses, we estimated RR and 95% confidence intervals by using both matched and unmatched methods (*6–8*). Since results from both analyses were similar (the differences being <10%), only the unmatched results are presented. Since the purpose of our study was to generate hypotheses for later confirmation, we made no effort to adjust for the multiple testing situation in which we examined numerous potential risk factors. Even if none of the factors examined were related to risk of RMS, an analysis such as this would be expected to generate *P*-values of less than 0.05 for 5 of every 100 variables. Thus for those variables that we have found to be significant, the actual significance level may be greater than our stated *P*-value.

RESULTS

SES.—The first group of variables examined were correlates of SES (table 2). We found the estimated RR associated with mothers' education beyond high school to be 0.3 ($P=0.04$); that for fathers was 0.5 ($P=0.13$). Similarly, the RR associated with mothers' having professional or managerial occupations was 0.4 and that for fathers was 0.5. The RR associated with annual family income of $10,000 or more was 0.5 ($P=0.09$). Whereas only one of these variables reached statistical significance at the 0.05 level, all RR were markedly low and deviated in the same direction from unity. This confluence of findings suggests that low SES is a risk marker for RMS.

Family medical history.—A second group of ques-

TABLE 1.—*Comparison of birth certificate information: Participating, lost and nonparticipating, and replacement controls*

Birth certificate information	Participating original controls[a]	Lost and non-participating controls[b]	Replacement controls[c]
Percentage of fathers with professional or managerial occupations	28	27	11
Mean years of fathers' education	11.6	10.5	12.0
Mean years of mothers' education	11.5	11.7	11.2
Mean age of fathers at subjects' birth	26.6	28.1	28.2
Mean age of mothers at subjects' birth	24.1	25.0	25.4
Percentage of married mothers	100	100	100
Percentage of mothers attended by physician at delivery	96	96	100
Mean gestational period, wk	38.5	38.4	39.1
Mean No. of prenatal visits	10.1	8.7	10.3

[a] No. = 70.
[b] No. = 36.
[c] No. = 29.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

TABLE 2.—*Childhood RMS risk factors: Socioeconomic indicators*

Risk factors	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
Mothers with ≥13 yr of education	4 (13)	31 (32)	0.3	0.1–0.9
Fathers with ≥13 yr of education	6 (19)	31 (33)	0.5	0.2–1.3
Mothers with professional or managerial occupations	3 (14)	18 (29)	0.4	0.1–1.6
Fathers with professional or managerial occupations	6 (21)	29 (34)	0.5	0.2–1.5
No. of families with annual income of $10,000 or more	14 (44)	59 (61)	0.5	0.2–1.1

tions dealt with family history of disease (table 3). The estimated RR for cancer in relatives of cases versus controls was 2.3 ($P=0.08$). However, when restricted to first-degree relatives—where recall would be more complete for both cases and controls—there was little difference in history of cancer between case and control families (RR = 0.7). Thus there was probably "selective recall" bias wherein case families are more apt to remember cancer in remote relatives.

We found an association of RMS with family history of asthma or allergies (RR = 2.5; $P=0.03$). When we restricted this analysis to first-degree relatives only, we found little change. Thus this finding is probably not subject to selective recall. Despite the more frequent history of asthma and allergies in case families, the RR for relatives' having received "allergy shots" was 0.4; however, this finding was not close to being statistically significant. Perhaps related to the asthma and allergies finding was our finding of an RR of 1.9 associated with a family history of frequent or serious infections. We also found an association with family history of anemia (RR = 2.1).

Gestational and delivery factors.—Several gestational and perinatal factors appeared to be associated with RMS (table 4). Mothers' use of antibiotics within 1 year preceding or during the subjects' gestation conferred an RR of 2.7 ($P=0.03$). Additionally, the RR associated with mothers' being over 30 years of age at the time of delivery was 2.6 ($P=0.06$). The RR associated with overdue versus normal delivery was 2.8 ($P=0.03$); that associated with premature delivery was 0.6. Forceps or cesarean section delivery conferred an RR of 2.4 ($P=0.10$). Thus the age of the mother, the length of her pregnancy, "assisted delivery," and gestational use of antibiotics may be risk markers for RMS. The RR for radiographic examination during pregnancy in case mothers versus control mothers was 0.5.

Neonatal history.—The RR associated with a history of neonatal jaundice was 0.3; that associated with neonatal conditions requiring medical treatment was 0.4 (table 5). However, the occurrence of neonatal problems was infrequent in cases and controls and none of the associations in this category was statistically significant at the 0.05 level.

Environmental exposures.—We also examined several environmental exposures (table 6). We found an RR of 3.2 associated with exposure to chemicals other than pesticides and rodenticides. This category includes exposures to such substances as solvents, paints, acids, bleaches, fertilizers, and gasoline. The only substances to which more than 1 case was exposed were chemical fertilizers. Three cases (9%) and 1 control (1%) had been exposed to fertilizers, yielding an RR of 10.0 (1.5–68, 95% confidence interval). Some of the cases had more than one type of chemical exposure. Similarly, living near a factory that emitted chemical pollution conferred an RR of 3.3 ($P=0.24$).

Diet.—The estimate of RR associated with the eating of organ meats (e.g., liver, brain, and tongue) was 3.7 ($P=0.004$) (table 7). Case families also used less animal fat (lard) in cooking than did control families (RR = 0.4). No other dietary factors appeared remarkably associated.

Immunization history.—Cases had received far fewer routine childhood immunizations than had controls (table 8). The RR for smallpox vaccination was 0.2 ($P=0.001$), for measles-mumps-rubella immunization 0.3, and for diphtheria-pertussis-tetanus immunization 0.7. We assessed the RR associated with overall immunization status in terms of "any immunizations" versus "no immunizations" and obtained an estimate of 0.7. We did not include the estimate of RR for poliomyelitis immunization because one of the cells in the related fourfold table contained a zero value. All 33 cases and 96 of 98 controls had received this immunization (RR = 0). In general, the RR deviated most from unity for those immunizations that might have a greater discretionary component on the part of the family (i.e., immunizations given latest in infancy).

Past medical history.—We found an RR of 4.1 (exact

TABLE 3.—*Childhood RMS risk factors: Family medical history*

Family history of	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
"Hereditary diseases"	17 (53)	53 (54)	1.0	0.4–2.2
Congenital birth defects	14 (42)	34 (34)	1.4	0.6–3.2
Cancer (all relatives)	26 (79)	61 (62)	2.3	0.9–5.8
Cancer (in parents or siblings only)	2 (6)	8 (8)	0.7	0.1–3.6
Heart disease	30 (91)	87 (88)	1.4	0.4–5.2
Frequent and/or serious infections	14 (42)	28 (28)	1.9	0.8–4.2
Asthma or allergies (all relatives)	23 (70)	47 (47)	2.5	1.1–5.8
Asthma or allergies (in parents or siblings only)	12 (36)	21 (21)	2.1	0.9–5.0
Any relative receiving "allergy shots"	3 (9)	20 (21)	0.4	0.1–1.3
Psychiatric and/or neurologic disease	14 (42)	34 (35)	1.4	0.6–3.1
Anemia	7 (21)	11 (11)	2.1	0.8–6.0
Death of subject's sibling	4 (12)	8 (8)	1.5	0.4–5.3

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

TABLE 4.—*Childhood RMS risk factors: Gestational and parturitional histories*

Risk factors	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
Mother's prior miscarriage	5 (19)	10 (11)	1.9	0.6–6.2
Mother's illness during pregnancy with subject	24 (73)	70 (74)	1.0	0.4–2.3
Mother's cigarette smoking during pregnancy	9 (28)	27 (28)	1.0	0.4–2.4
Mother's consumption of alcohol during pregnancy	4 (13)	16 (17)	0.7	0.2–2.4
Radiographic examination during pregnancy	2 (6)	11 (12)	0.5	0.1–2.4
Weight gain during pregnancy (>11.3 vs. ≤11.3 kg)	10 (34)	32 (36)	0.9	0.4–2.2
Medications used by mother during and/or 1 yr prior to pregnancy:				
Aspirin	3 (72)	64 (70)	1.1	0.5–2.7
Antibiotics	13 (43)	19 (22)	2.7	1.1–6.5
Pain or cold remedies	10 (34)	28 (32)	1.1	0.5–2.7
Tranquilizers	2 (7)	5 (5)	1.3	0.2–6.9
Oral contraceptives or other birth control methods	8 (25)	23 (24)	1.0	0.4–2.6
Drugs for menstrual disorders or infertility	2 (6)	5 (5)	1.2	0.2–6.4
Length of pregnancy:				
Premature delivery (vs. normal)	4 (18)	19 (24)	0.7	0.2–1.8
Overdue delivery (vs. normal)	10 (36)	13 (18)	2.6	1.1–7.1
Length of labor (>10 hr vs. ≤10 hr)	10 (36)	25 (27)	1.5	0.6–3.7
Mother's age at subject's birth (>30 vs. ≤30 yr)	9 (27)	12 (13)	2.6	1.0–6.8
Type of delivery (forceps or cesarean vs. other)	8 (24)	11 (12)	2.4	0.9–6.6
Place of delivery (hospital vs. home)	31 (94)	93 (94)	1.0	0.2–5.2

TABLE 5.—*Childhood RMS risk factors: Neonatal history*

Risk factors	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
Birth weight (>3.4 vs. ≤3.4 kg)	14 (44)	40 (42)	0.9	0.5–2.4
Birth length (>50 vs. ≤50 cm)	7 (35)	21 (48)	0.6	0.2–1.8
Congenital malformations	8 (24)	18 (19)	1.4	0.5–3.5
Circumcision (males)	19 (83)	58 (89)	0.6	0.2–2.2
Conditions requiring medical treatment	2 (6)	12 (13)	0.4	0.1–2.0
Newborn infections	1 (3)	4 (4)	0.7	0.1–6.5
Jaundice	1 (3)	8 (8)	0.3	0.04–2.6
Diarrhea and/or unusual vomiting	2 (6)	8 (9)	0.7	0.1–3.4
Feeding problems	1 (3)	5 (5)	0.6	0.1–4.8

$P=0.05$) associated with prior history of whooping cough and of 4.3 for impetigo (exact $P=0.07$) (table 8). There was also an increased history of measles (RR = 2.0) and of asthma (RR = 2.5) in cases. However, there was no association between RMS and history of infectious diseases for which no immunizations are available, such as otitis media or chickenpox (RR = 0.9 for both). The RR associated with scarlet fever was 0.5.

Miscellaneous factors.—Table 9 summarizes our evaluation of a number of miscellaneous potential risk factors. Fathers who were ever-smokers (relative to those who were never-smokers) conferred an RR of 3.9 ($P=0.003$). This finding was in contrast to the findings of an RR of 0.8 for children of mothers who were ever-smokers and of 1.0 for children of mothers who smoked cigarettes during their pregnancy.

TABLE 6.—*Childhood RMS risk factors: Childhood environment*

Risk factors	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
No. of people dwelling in home (>5 vs. ≤5)	4 (12)	15 (15)	0.8	0.2–2.5
No. of rooms in homes (≤5 vs. >5)	21 (64)	53 (55)	1.5	0.6–3.3
Sharing of bedroom by subject	25 (78)	74 (75)	1.2	0.5–3.1
Any pet animals	27 (82)	85 (86)	1.7	0.3–2.1
Dogs	24 (75)	75 (77)	0.9	0.3–2.2
Cats	16 (50)	41 (42)	1.4	0.6–3.0
Indoor plumbing	27 (82)	74 (76)	1.5	0.5–4.0
Water source (city or town water vs. other)	13 (39)	36 (36)	1.1	0.5–2.6
Pesticide exposure	3 (9)	6 (6)	1.5	0.4–6.5
Rodenticide exposure	1 (3)	3 (3)	1.0	0.1–9.9
Other chemical exposures	7 (22)	8 (8)	3.2	1.1–9.2
Any exposure to pollution from factories or plants	6 (19)	11 (11)	1.9	0.6–5.6
Exposure to chemicals from factories	2 (6)	2 (2)	3.3	0.5–22
Exposure to fumes from factories	3 (10)	9 (9)	1.0	0.3–4.2
Exposure to dust from factories	1 (3)	3 (3)	1.0	0.1–10.5
Exposure to waste from factories	2 (6)	5 (5)	1.2	0.2–6.8
Subject's travel abroad	2 (6)	5 (5)	1.2	0.2–6.6
Exposure to playmate who had cancer	1 (3)	2 (2)	1.5	0.1–17

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TABLE 7.—*Childhood RMS risk factors: Diet*

Risk factors	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
Subject's egg consumption (>4 vs. ≤4/wk)	12 (41)	35 (36)	1.3	0.5–2.9
Use of butter vs. margarine	2 (6)	6 (6)	1.0	0.2–5.4
Family's use of animal fat vs. vegetable oil in cooking	2 (6)	13 (15)	0.4	0.1–2.0
Formula vs. breast feeding in infancy	23 (72)	61 (63)	1.5	0.6–3.6
Daily milk consumption (>0.95 vs. ≤0.95 liter)	5 (17)	19 (20)	0.8	0.3–2.3
Use of whole vs. other milk	22 (73)	71 (75)	0.9	0.4–2.4
Luncheon meat consumption (>4 vs. ≤4 times/mo)	17 (55)	47 (50)	0.8	0.4–1.9
Hotdog consumption (>4 (vs. ≤4 times/mo)	11 (34)	29 (31)	1.2	0.5–2.8
Ham consumption (>4 vs. ≤4 times/mo)	3 (10)	8 (9)	1.1	0.3–4.5
Bacon consumption (>4 vs. ≤4 times/mo)	20 (63)	48 (52)	1.5	0.7–3.5
Sausage consumption (>4 vs. ≤4 times/mo)	13 (41)	37 (40)	1.0	0.4–2.3
Organ meat consumption	21 (70)	37 (39)	3.7	1.5–8.3
Frequency of family's purchase of 1 pound of salt (once/mo or more vs. other)	11 (35)	33 (34)	1.1	0.4–2.5
Subject's use of salt at table (yes vs. no)	19 (59)	48 (52)	1.4	0.6–3.1
Subject's use of food substitutes	5 (16)	18 (18)	0.8	0.3–2.4
Family's use of diet foods or beverages	2 (6)	6 (6)	1.0	0.2–5.2
Family's use of saccharin	7 (22)	15 (16)	1.5	0.6–4.1
Family consumption of meats:				
Beef (>2 vs. ≤2 times/wk)	16 (50)	53 (54)	0.9	0.4–1.9
Pork (>2 vs. ≤2 times/wk)	9 (28)	19 (20)	1.6	0.6–4.0
Chicken (>2 vs. ≤2 times/wk)	7 (22)	17 (17)	1.4	0.5–3.6
Fish (>2 vs. ≤2 times/wk)	4 (13)	16 (16)	0.7	0.2–2.4

Assessment of confounding by SES.—Because we were concerned that some of our findings might be confounded by SES, we controlled for family income and fathers' education and occupation in a matched logistic regression analysis of fathers' cigarette smoking and of smallpox vaccination status. In the analysis of fathers' smoking, we obtained an adjusted RR of 2.8 ($P=0.07$). In the analysis of smallpox vaccination, we obtained an adjusted RR of 0.2 ($P=0.009$). Due to incomplete data, the number of subjects included in these analyses was smaller than that in the univariate analyses.

TABLE 8.—*Childhood RMS risk factors: Subject's medical history*

Risk factors	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
Smallpox vaccination	21 (66)	88 (90)	0.2	0.1–0.6
Measles-mumps-rubella immunization	29 (91)	93 (97)	0.3	0.1–1.5
Diphtheria-tetanus-pertussis immunization	32 (97)	96 (98)	0.7	0.1–7.6
Overall immunization status (ever vs. never)	32 (97)	96 (98)	0.7	0.1–7.6
Measles	14 (42)	25 (27)	2.0	0.9–4.6
Mumps	13 (39)	33 (34)	1.3	0.6–2.9
Rubella	5 (16)	21 (23)	0.6	0.2–1.8
Pertussis	5 (15)	4 (4)	4.1	1.1–15
Chickenpox	23 (70)	70 (73)	0.9	0.4–2.0
Scarlet fever	1 (3)	6 (6)	0.5	0.1–3.9
Hepatitis	1 (3)	5 (5)	0.6	0.1–5.0
Pneumonia	2 (6)	8 (8)	0.7	0.2–3.6
"Strep throat"	10 (30)	28 (29)	1.1	0.4–2.5
Otitis media	10 (30)	31 (32)	0.9	0.4–2.2
Impetigo	4 (12)	3 (3)	4.3	1.0–18
Warts	5 (16)	12 (14)	1.2	0.4–3.6
Asthma	3 (9)	4 (4)	2.3	0.5–11

DISCUSSION

This study uncovered a number of potential risk factors for RMS. First, we found a confluence of associations with variables related to SES. We found that both mothers and fathers of cases had received less education than control parents, that case parents' occupations tended to be of a lower income and prestige level, and that total family income for cases was lower than that for controls. Whereas only mothers'

TABLE 9.—*Childhood RMS risk factors: Miscellaneous factors*

Risk factors*	No. of cases (%)	No. of controls (%)	RR	95% confidence interval
Fathers who smoke cigarettes (ever)	23 (77)	40 (46)	3.9	1.5–9.6
Mothers who smoke cigarettes (ever)	8 (26)	29 (31)	0.8	0.3–2.0
Religion (Protestant vs. other)	26 (81)	68 (81)	1.0	0.4–2.9
Birth order (first vs. other)	13 (39)	41 (41)	0.9	0.4–2.1
No. of children in sibship (>5 vs. ≤5)	7 (21)	14 (14)	1.6	0.6–4.5
Father's age at subject's birth (>30 vs. ≤30 yr)	7 (22)	25 (26)	0.8	0.3–2.0
Marital status of mother (married vs. other)	23 (70)	73 (75)	0.8	0.3–1.8
Current residence (in town of ≥5,000 vs. <5,000)	20 (61)	61 (63)	0.9	0.4–2.0
Farm residence (ever vs. never)	2 (6)	6 (6)	1.0	0.2–5.2
Current residence (outside an SMSA vs. in an SMSA)	23 (70)	62 (64)	1.3	0.6–3.0

* SMSA = standard metropolitan statistical area.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtnx0000

educational level showed a statistically significant association with RMS and family income was at the margin of statistical significance, all of these factors, in the aggregate, suggested that low SES is a risk marker for RMS. Our characterization of lost and nonparticipating controls and comparisons with participating controls suggested that if our selection and location procedures introduced any SES bias, it was of a conservative nature.

Other studies that examined childhood cancer risk in relation to social class have dealt primarily with leukemia. Stewart et al. (*9*) found no association between social class (as indexed by father's occupation alone) and the risk of leukemia or of all childhood cancers. Fasal and co-workers (*10*), using birth and death certificates of children who died of leukemia, found a small but statistically significant increase in leukemia risk for children of high social class (RR = 1.33; χ_1^2 = 4.58), with social class defined by fathers' occupation. Although prior studies have found no or weak associations between social class and childhood cancer risk, these studies have been limited by having minimal data available for the classification of families' social class.

Perhaps our most salient finding is the strong association between RMS and fathers' cigarette smoking. This finding has two possible explanations. First, a direct carcinogenic effect may be introduced either in a prezygotic manner or by passive inhalation of cigarette smoke by the patients. In support of a direct effect are two studies suggesting a mutagenic effect of fathers' cigarette smoking. Evans and co-workers (*11*) found morphologic sperm abnormalities in cigarette smokers, and Mau and Netter (*12*) showed a twofold increase in the occurrence of severe malformations in children of fathers who were heavy cigarette smokers. The second interpretation relates to SES. Wynder and Hoffmann (*13*) showed that cigarette smoking is inversely related to educational level among men but not among women. Thus the positive finding for fathers but not for mothers may relate to our observation that low SES may be a marker of increased RMS risk. However, the results of our matched logistic regression analysis suggest that this is not a likely explanation. We believe the first hypothesis deserves further consideration.

Most of the numerous studies of mothers' cigarette smoking and risk of malformation in their offspring have shown no or weakly positive associations. The U.S. Surgeon General's 1979 Report on Smoking and Health (*14*) concluded: "There is no convincing evidence that maternal smoking increases the incidence of congenital malformations. Results of published studies, reviewed in the 1973 report (*15*), show relative risks for smokers versus nonsmokers ranging from 0.51 to 1.55." Thus if Mau and Netter's findings (*12*) prove valid, our observation of a possible association between fathers' (but not mothers') cigarette smoking and risk of RMS appears even more worthy of further study.

Several studies have directly examined cancer risk of children in relation to their parents' smoking status (*9, 16–18*). All have shown little or no association between mothers' smoking and cancer risk in their offspring and therefore are consistent with our findings. We found only one study that evaluated the association between fathers' smoking and risk of cancer among their children. Stewart et al. (*9*) found that fathers of children with leukemia were only slightly more apt to be smokers than those of control children, but the authors point out that their analysis was crude.

We found internal consistency in our study when we examined immunization status and history of infectious diseases. Cases had received remarkably fewer immunizations than had controls and, conversely, they had contracted more of those diseases preventable by immunization. The association of RMS with impetigo, a disease associated with poor hygiene, was also interesting. Our finding of an association with history of pertussis is similar to an observation made by Bross and Natarajan (*19*) in a study of children with leukemia. These investigators found a twofold increase in leukemia risk for children with a history of antecedent bacterial infection (defined as "pneumonia, whooping cough, or dysentery").

Our findings of fewer immunizations in cases are similar to those in Neumann's study (*20*) of children dying of cancer in Baden-Württemberg, Federal Republic of Germany. Neumann found statistically significantly less diphtheria immunization in case children than matched controls (RR = 0.25). His cases had less tetanus (RR = 0.46), poliomyelitis (RR = 0.75), and BCG (RR = 0.69) immunizations but more smallpox vaccination (RR = 1.28) than did his controls, though these differences were not statistically significant. All of his findings are consistent with ours except for those with regard to smallpox vaccination. This would suggest that the specific immunizations are not themselves risk factors, but that immunization status per se is a risk marker for childhood cases.

We found a notable association with exposure to chemicals and chemical pollution. Cases also appeared to have eaten more organ meats than did controls and somewhat more pork (RR = 1.6). The increased consumption of organ meat and pork may be interrelated in that NC farmers (and rural families) who slaughter their own pigs will usually utilize all organ and "variety" meats.

We found associations between RMS and several gestational and parturitional factors. These include a positive association with an overdue delivery and, conversely, a negative association with premature delivery of the propositus. Additionally, use of forceps and cesarean section in the delivery of subjects and use of antibiotics by mothers during the year and 9 months preceding the birth of their children appear to be risk markers of RMS. We found an interesting association with mothers' age at birth of subjects. Similar observations were made in earlier studies, which showed that mothers of children with leukemia were significantly older than mothers of controls (*9, 16, 21*). One of these

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studies (*9*) showed that the increased risk of leukemia with increasing maternal age was independent of the occurrence of Down's syndrome. Another study showed a "consistent, although not statistically significant, trend toward increasing rates with increasing maternal age" for all childhood cancers (*21*).

The findings of an association with history of asthma and allergies in families and of an RR of 2.3 for history of asthma in subjects suggest that immunologic factors play a role in the etiology of RMS. Bross and Natarajan (*19*), in their case-control study of childhood leukemia, similarly found a three-fold increase in risk associated with subjects' history of antecedent allergic diseases (asthma and hives). Manning and Carroll (*16*) showed similar results more than 20 years ago. They also found a statistically significant association between risk of childhood leukemia (and lymphoma) and mothers' history of having had allergic diseases. However, there was no increased history of allergies for children with other cancers or their mothers.

In summary, we have found a number of potential risk factors for childhood RMS. We found immunization status, fathers' cigarette smoking, diet, chemical exposures, mothers' age, gestational factors, asthma, and SES to be associated with RMS. In particular, we believe that the association with fathers' smoking is deserving of further evaluation. The aggregate of our findings implies that environmental factors may play an important role in the etiology of childhood RMS. We must, however, caution that this is the first case-control study of this rare cancer and that our study size was small. Further investigation is needed to confirm our findings in another setting.

We believe that the issue of environmental factors in the etiology of childhood cancers has not been explored adequately. The relatively short latent periods between potential etiologic exposures and disease manifestation in children provide unique opportunities for the study of environmental factors. Similar case-control studies of other childhood cancers might provide important new etiologic leads.

REFERENCES

(*1*) Young JL Jr, Miller RW. Incidence of malignant tumors in U.S. children. J Pediatr 1975; 86:254-258.

(*2*) Jones PM. Cancer in children. Practitioner 1979; 222:221-228.

(*3*) Li FP, Fraumeni JF Jr. Rhabdomyosarcoma in children: Epidemiologic study and identification of a familial cancer syndrome. J Natl Cancer Inst 1969; 43:1365-1373.

(*4*) Miller RW, Dalager NA. Fatal rhabdomyosarcoma among children in the United States, 1960-69. Cancer 1974; 34:1897-1900.

(*5*) Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 1969; 71:747-752.

(*6*) Miettinen OS. Estimability and estimation in case-referent studies. Am J Epidemiol 1976; 103:226-235.

(*7*) ———. Simple interval-estimation of risk ratios. Am J Epidemiol 1974; 100:515-516.

(*8*) ———. Estimation of relative risk from individually matched series. Biometrics 1970; 26:75-86.

(*9*) Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. Br Med J 1958; 1:1495-1508.

(*10*) Fasal E, Jackson EW, Klauber MR. Birth characteristics and leukemia in childhood. J Natl Cancer Inst 1971; 47:501-509.

(*11*) Evans HJ, Fletcher J, Torrance M, Hargreave TB. Sperm abnormalities and cigarette smoking. Lancet 1981; 1:627-629.

(*12*) Mau G, Netter P. Die Auswirkungen des väterlichen Zigarettenkonsums auf die perinatale Sterblichkeit und die Missbildungshaufigkeit. Dtsch Med Wochenschr 1974; 99:1113-1118.

(*13*) Wynder EL, Hoffmann D. Tobacco and health. A societal challenge. N Engl J Med 1979; 300:894-903.

(*14*) U.S. Public Health Service. Smoking and health. A report of the Surgeon General. Washington, D.C.: U.S. Govt Print Off; 1979, part 8:39 [DHEW publication No. (PHS)79-50066].

(*15*) U.S. Public Health Service. The health consequences of smoking. A report of the Surgeon General. Washington, D.C.: U.S. Govt Print Off, 1973:136-137 [DHEW publication No. (HSM) 73-8704].

(*16*) Manning MD, Carroll BE. Some epidemiologic aspects of leukemia in children. J Natl Cancer Inst 1957; 19:1087-1094.

(*17*) Neutel CI, Buck C. Effect of smoking during pregnancy on the risk of cancer in children. J Natl Cancer Inst 1971; 47:59-65.

(*18*) Gold E, Gordis L, Tonascia J, Szklo M. Risk factors for brain tumors in children. Am J Epidemiol 1979; 109:309-319.

(*19*) Bross ID, Natarajan N. Leukemia from low-level radiation. Identification of susceptible children. N Engl J Med 1972; 287: 107-110.

(*20*) Neumann G. Zusammenhang zwischen Schutzimpfungen und bösartigen Neubildungen im Kindesalter? Med Klin 1980; 75: 72-75.

(*21*) MacMahon B, Newill VA. Birth characteristics of children dying of malignant neoplasms. J Natl Cancer Inst 1962; 28: 231-244.

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Exposure to Cigarette Smoke and Cervical Cancer

To the Editor.—We would like to comment on the article by Slattery et al[1] entitled "Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer."

In case-control studies there is always the danger of overmatching or undermatching in selection of control subjects. In this report, there clearly is undermatching of control patients with regard to important risk factors including sexual activity, religious background, and education. For example, 52% of control subjects vs only 10% of case subjects reported having fewer than two sexual partners; 75% of control subjects but only 49% of case subjects were high school graduates; and 58% of control subjects vs 18% of case subjects were frequent churchgoers. Since the previously mentioned risk factors are correlated highly with one another as well as with active and passive smoking, the risk estimates relating smoking and cervical cancer may be subject to substantial bias and confounding. This has been demonstrated in logistic regression analyses when the variables show high multicolinearity.[2] It is fallacious to expect multivariate techniques such as logistic regression to correct all the resultant confounding and biases. The effect of adjustment on odds ratios is far greater than expected in case-control studies of this sort, as, for example, the decrease from 14.84 to 2.96 for passive smoke exposure. In fact, the adjusted odds ratios are probably no more than the leftover effect of variables controlled imperfectly by logistic regression.

Another potential source of confounding for which there is a complete lack of information concerns the smoking behavior and sexual activities of male sexual partners. The apparent association between cervical cancer and environmental smoke exposure may, in fact, be the result of increased exposure to papillomaviruses or herpes simplex virus 2 through contact with male sexual partners who smoke, since one might expect smokers to be generally more sexually active than nonsmokers, and case patients are more sexually active than control subjects.

In addition, when case and control subjects are compared with regard to the number of sexual partners, the actual difference could be underestimated easily because of the expected tendency among case subjects to underreport their higher level of sexual activities.

Furthermore, no information is given about the age at which sexual activities began, although early promiscuity is a known risk factor for cervical cancer and probably is related to smoking as well. This important issue of sexual behavior vis-à-vis smoking and cervical cancer is confounded further by the fact that monogamous and celibate participants were combined into a single category in the analyses, although their exposure to both environmental smoke and sexually transmitted infections clearly is not equal.

Finally, a comment on biologic plausibility. As stated in the article, colleagues at our institute have reported the presence of cotinine in cervical mucosa.[3] However, the mean concentration of cotinine in passive smokers is less than 1% of that observed in active smokers. Furthermore, no nitrosamines or other carcinogens thus far have been isolated successfully from cervical mucosa, even in heavy smokers. It is highly unlikely that the carcinogenic effect of passive and active tobacco smoke exposures is approximately equal (with odds ratios of 2.96 and 3.42, respectively), as reported by the authors.

In view of the previously mentioned considerations, the classification of passive smoke exposure as a risk factor for cervical cancer seems premature.

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1. Slattery ML, Robison LM, Schuman KL, et al. Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *JAMA*. 1989;261:1593-1598.
2. McGee D, Reed D, Katsuhiko Y. The results of logistic analyses when the variables are highly correlated. *J Chronic Dis*. 1964;37:713-719.
3. Haley NJ, Hoffmann D, Wynder EL. Uptake of tobacco smoke components. In: Hoffmann D, Harris CC, eds. *Mechanisms in Tobacco Carcinogenesis*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory; 1986:3.

In Reply. — Control patients were matched to case patients by age in our study, while sexual history, education, and church attendance (to help control for sexual activity) were controlled in the smoking analyses so that they also could be examined as independent risk factors in other analyses.[1] Because of the risk of cervical cancer associated with these variables,[2] major differences in their distribution between case and control subjects were noted. These variables, although associated, did not present, in the analysis, a problem of multicolinearity. While logistic regression models have the capability to control for confounding, they can only control to the extent that the data are accurate. Thus, biased risk estimates could result if important confounding variables were reported inaccurately, although they were controlled in the analyses. While there is the possibility that sexual history is reported inaccurately, we do not believe that case patients reported differently than control patients because they were unaware that we were studying cervical cancer. The reported number of sex partners of the woman was used to control for sexual activity patterns; results were qualitatively the same when adjusting for the number of sexual partners of the man; age at first intercourse was not related to cervical cancer after controlling for the number of sexual partners.[1] It is possible that either human papillomavirus or type-specific herpes simplex virus 2 may be partially confounding the observed association; at present, we are unable to explore this issue in more detail.

At this point, we can only speculate how active or passive smoking can biologically be related to cervical cancer. The risk estimates observed for cigarette smoking are similar to those reported elsewhere in the literature, which gives credence to our findings. The risk estimates associated with passive smoking should not be inflated or more biased than those associated with actual smoking because of inadequate recall or uncontrolled confounding. Based on our results, we believe that this association should be verified in other studies. Lastly, as pointed out by Dr Layde in his editorial,[2] while we do not know of a biologic mechanism for either active or passive smoking to be related to cervical cancer, we do know that cigarette smoking is harmful to health. The message to the public, as a result of this study, is one that reinforces the message that smoking is detrimental to health.

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1. Slattery ML, Overall JC Jr, Abbott TM, et al. Sexual activity, contraception, genital infections and cervical cancer: support for a sexually transmitted disease hypothesis. *Am J Epidemiol*. In press.
2. Layde PM. Smoking and cervical cancer: cause or coincidence? *JAMA*. 1989;261:1631-1633.

Amateur Boxing

To the Editor.—I was disappointed and dismayed by the misleading article on boxing in the January 6 issue of *JAMA*.[1] Juan Antonio Samarach, president of the International Olympic Committee, publicly stated his support for including boxing in the Olympic program. The committee's investigation of boxing was directed toward reviewing the scoring system.

It is unfair to lump all types of boxing together. Professional and amateur boxing have vastly different rules, objectives, and requirements. No matter what television commentators might say, the style and technique are not the same. To combine events and actions of the two types of boxing in one article totally misrepresents the facts. Moreover, the boxing programs for police

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Prenatal Exposure to Parents' Smoking and Childhood Cancer

Esther M. John,[1,2] David A. Savitz,[1] and Dale P. Sandler[3]

The relation between parents' tobacco smoking prior to birth and cancer in the offspring was investigated with the use of data from a case-control study. Incident cases included all children (aged 0–14 years) diagnosed in Denver, Colorado from 1976 to 1983. Controls were selected through random digit dialing, and matched to cases on age, sex, and geographic area. Information on smoking by parents and other household members was obtained by personal interview for 223 cases and 196 controls. After adjustment for father's education, mother's smoking during the first trimester of pregnancy was associated with an increased risk for all cancers combined (odds ratio (OR) = 1.3, 95% confidence interval (CI) 0.7–2.1), acute lymphocytic leukemia (OR = 1.9, 95% CI 0.9–4.1), and lymphomas (OR = 2.3, 95% CI 0.8–7.1). Adjusting for father's education, associations with father's smoking in the absence of mother's smoking were found for all cancers combined (OR = 1.2, 95% CI 0.8–2.1), acute lymphocytic leukemia (OR = 1.4, 95% CI 0.6–3.1), lymphomas (OR = 1.6, 95% 0.5–5.4), and brain cancer (OR = 1.6, 95% CI 0.7–3.5). In spite of imprecision resulting from small numbers of cases in diagnostic subgroups, these results are suggestive of a possible influence of parents' smoking on childhood cancer. *Am J Epidemiol* 1991;133:123–32.

brain neoplasms; child; leukemia; smoking

Effects of maternal smoking on the developing fetus have been addressed in numerous studies, and increased risks of adverse pregnancy outcomes, including spontaneous abortion, low birth weight, preterm delivery, and perinatal death, have been reported (1). Biochemical measurements of cigarette smoke constituents in the placenta (2), amniotic fluid (3–5), and fetal blood (6, 7) of both actively and passively smoking mothers demonstrate the transplacental passage of cigarette smoke constituents. Two exposure pathways therefore determine fetal exposure to cigarette smoke: the mother's smoking during pregnancy and her exposure to smoking by others in the home (e.g., the child's father, other household members) or outside the home (e.g., at the workplace).

Prenatal exposure to mother's cigarette smoking may also increase the risk of cancer in the offspring. Associations with maternal smoking during pregnancy have been reported for all childhood cancers combined

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Abbreviations: CI, confidence interval; OR, odds ratio.

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This study was part of a research program to determine the possible adverse health effects resulting from exposure to the electric and magnetic fields of overhead high voltage transmission lines. The program was administered by the State of New York Department of Health and Health Research, Inc.

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(8), leukemia (9), and brain cancer (10). Twofold risks for acute lymphocytic leukemia, non-Hodgkin's lymphoma, and Wilms' tumor have been associated with maternal smoking of 10 or more cigarettes per day (11). A number of studies, however, found no association between maternal smoking and childhood cancer (12–21). In laboratory animals, transplacental exposure to various cigarette smoke constituents has been shown to increase the incidence of tumors at several sites (22). In hamsters, tumors have been induced by transplacental exposure to cigarette smoke condensate (23).

Few studies have addressed the risk of childhood cancer associated with father's smoking. Associations have been reported for paternal smoking during pregnancy and rhabdomyosarcoma (24), for paternal smoking any time prior to birth and neuroblastoma (20), and for mothers living with a smoker during pregnancy and brain cancer (13). In other studies, no associations between childhood cancer and paternal smoking were found (16–18, 21, 25). The mechanisms involved are uncertain but fetal exposure to father's smoking, albeit at a lower dose, may occur through the passively smoking mother. Another possibility is an effect of father's smoking on paternal germ cells (24). Exposure of male rats to ethylnitrosourea before mating was found to increase the incidence of neurogenic tumors in the offspring (26). Mutagenic effects in germ cells may result from cigarette smoking (27), thus supporting the plausibility of carcinogenic effects through damage to paternal germ cells.

Further study of this relation is warranted, given the high prevalence of fetal exposure to cigarette smoke. In the 1980 National Natality Survey, 31 percent of married mothers of liveborn infants smoked before pregnancy and 26 percent of married mothers continued to smoke during pregnancy (28). Furthermore, passive smoking of at least one hour per week has been reported for 63 percent of nonsmoking adults (29).

We report here results of a study of childhood cancer which collected data on both mother's and father's tobacco smoking during the prenatal period. Unlike other studies, we were better able to identify a truly unexposed group by obtaining complete household smoking histories for the time from conception to the child's diagnosis.

MATERIALS AND METHODS

The data for this analysis came from a case-control study of childhood cancer and exposure to electromagnetic fields (30). Incident cancer cases diagnosed from 1976 to 1983, aged 0–14 years, and residing in the Denver Standard Metropolitan Statistical Area at the time of diagnosis were eligible. The cases were identified through the Colorado Central Cancer Registry and review of medical records of hospitals that did not provide data to the registry for the entire case ascertainment period (31). The 356 eligible cases who were identified yielded 61 (17.1 percent) untraceable, 31 (8.7 percent) respondent refusals, four (1.1 percent) physician refusals, and eight (2.2 percent) not interviewed for other reasons such as language difficulties or incompetence. Interviews were completed for 252 (70.8 percent) eligible cases, including 73 leukemias, 48 brain cancers, 26 lymphomas, 26 soft tissue sarcomas, and 79 other tumors. The group of "other tumors" consisted primarily of neuroblastomas, bone cancer, endocrine tumors, and a very small number of several other types, none of which was sufficiently common to be analyzed separately.

Controls were selected through random digit dialing and individually matched to cases on age (plus or minus 3 years), sex, and telephone exchange area. Controls were assigned the identical age at diagnosis as the corresponding case to ensure equal reference periods for exposures. The 278 controls identified through random digit dialing reflect an estimated response proportion of 78.6 percent (30). Among the eligible controls, 55 (19.8 percent) refused to participate and interviews were conducted with 222 (79.9 percent). The overall response is a product of the response to random digit dialing selection (78.6 percent) and the proportion with completed interviews among

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those selected (79.9 percent), or 62.8 percent overall.

Structured interviews were administered in the participants' homes by trained interviewers from 1984 to 1985. Telephone interviews were conducted for families no longer residing in the Denver area or those who refused an in-home interview (11 percent of cases and 2 percent of controls). Information was collected on potential risk factors for childhood cancer, including smoking by both parents and other household members.

The mother's cigarette smoking status was assessed separately for the 3 months prior to the child's conception and for each trimester of pregnancy. If the mother smoked at any time during the year prior to the child's birth, information was obtained on the usual number of cigarettes smoked per day. The father's smoking of cigarettes, cigars, or pipes was assessed for the year prior to the child's birth. Among smokers, the usual number of cigarettes smoked per day was assessed. Information on the presence of other smokers in the household was derived from questions regarding the number of regular smokers at each residence from conception to the time of the child's diagnosis.

This analysis was restricted to 223 cases and 196 controls. Excluded were children for whom the interview could not be conducted with a biologic parent (nine cases and 10 controls), children with missing information on parents' smoking (12 cases and nine controls), and children whose parents did not smoke but who were exposed to smoking by other household members (eight cases and seven controls). The risk of childhood cancer was examined in relation to several exposure measures, including mother's and father's smoking during the 12 months prior to birth regardless of their spouse's smoking status, mother's and father's smoking before birth in the absence of their spouse's smoking, and smoking by both parents before birth. For comparison with the exposed, a single unexposed group was defined by the absence of exposure to smoking by either parent or other household members from the period starting one year before birth through the time of diagnosis. Based on information on parents' smoking before birth and on the number of smokers in the household, 82 unexposed cases and 86 unexposed controls were identified.

Since the selection of controls by pair-matching on age, sex, and geographic area was not intended as a unique individual match, unmatched analyses were conducted. When individual matching is based on such general attributes, precision is lost if the individual matching is retained in the analysis (32). For all cancers combined and for major diagnostic subtypes, odds ratios and test-based 95 percent confidence intervals were computed to assess crude associations with mother's and father's smoking (33). To identify potentially confounding factors, conditional associations with childhood cancer and with mother's and father's smoking were evaluated. For variables found to be associated with both the outcome and exposure, stratified analyses were performed for all cancers combined and major diagnostic subtypes. Adjusted odds ratios were computed using the Mantel-Haenszel approach (34).

RESULTS

Sociodemographic characteristics of cases and controls included in this analysis are shown in table 1. Cases and controls were similar with regard to year of birth, sex, age at diagnosis, and mother's race and age. However, control fathers had a higher level of education than case fathers.

Exposure to mother's cigarette smoking during the 3 months prior to conception was reported for 145 children (35 percent). Of these, 109 children continued to be exposed to mother's smoking during the first trimester of pregnancy, and 97 during the entire pregnancy. Prenatal exposure to father's tobacco smoking (cigarettes, cigars, or pipes) during the year prior to the child's birth was reported for 220 children (53 percent).

Mothers' and fathers' smoking was highly correlated. Of the 109 children exposed to mother's smoking during the first trimester of pregnancy, 88 (81 percent) were also ex-

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TABLE 1. Sociodemographic characteristics of childhood cancer cases and controls, Denver, 1976–1983

	Cases (n = 223)		Controls (n = 196)	
	No.	%	No.	%
Year of birth				
1960–1972	96	43	83	42
1973–1985	127	57	113	58
Sex				
Male	130	58	118	60
Female	93	42	78	40
Age (years) at diagnosis				
<1	30	13	21	11*
1–2	51	23	41	21
3–4	30	13	31	16
5–9	48	22	42	21
10–14	64	29	61	31
Mother's race				
White	192	86	174	89
Black	18	8	20	10
Other	12	5	2	1
Mother's age (years) at child's birth				
15–19	22	10	9	6
20–34	186	83	173	88
35+	15	7	14	7
Father's education				
High school or less	89	41	64	33
Some college	51	23	42	21
College graduate	79	36	90	46

* Based on age at diagnosis of corresponding case.

posed to father's tobacco smoking. One hundred and five children were exposed to father's smoking alone, thus allowing examination of the association of paternal smoking with childhood cancer in isolation from maternal smoking.

Crude associations of childhood cancer with prenatal exposure to mother's cigarette smoking are presented in table 2. Classifying children as prenatally exposed if their mother smoked cigarettes during the 3 months prior to conception, an odds ratio (OR) of 1.3 (95 percent confidence interval (CI) 0.8–2.0) was found for all cancers combined. Odds ratios were highest for acute lymphocytic leukemia (OR = 2.1, 95 percent CI 1.0–4.3) and lymphomas (OR = 1.9, 95 percent CI 0.7–5.2), although the number of lymphoma cases was small (n = 17). There was no association of mother's smoking with solid tumors, including brain cancer (OR = 0.9), soft tissue sarcoma (OR = 1.2), and other tumors (OR = 1.1). Restricting the exposed to children whose mothers continued to smoke cigarettes during the first trimester of pregnancy increased the odds ratios for all cancers combined (OR = 1.5), acute lymphocytic leukemia (OR = 2.3), and lymphomas (OR = 2.5) (table 2). Further restriction of the exposed to children whose mother smoked throughout pregnancy increased the odds ratio for acute lymphocytic leukemia to 2.5 and that for lymphomas to 2.7.

Dose-response relations were evaluated by the reported number of cigarettes smoked per day (table 2). For all cancers combined, the odds ratios for lighter smoking (10 or fewer cigarettes per day) and for heavier smoking (11 or more cigarettes per day) were 1.3 (95 percent CI 0.7–2.7) and 1.7 (95 percent CI 1.0–3.0), respectively, for maternal smoking during the first trimester, suggesting a dose-response gradient. A similar trend for maternal smoking during the first trimester was found for acute lymphocytic leukemia, with an odds ratio of 1.9 (95 percent CI 0.7–5.6) for lighter smoking and

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an odds ratio of 2.6 (95 percent CI 1.1–6.3) for heavier smoking.

For all cancers combined, father's tobacco smoking (cigarettes, cigars, or pipes) during the year prior to the child's birth produced a crude odds ratio of 1.3 (95 percent CI 0.9–2.0) (table 3). The strongest associations were found for acute lymphocytic leukemia (OR = 1.9, 95 percent CI 1.0–3.7) and lymphomas (OR = 1.9, 95 percent CI 0.7–4.8). A slightly elevated odds ratio was also found for brain cancer (OR = 1.4, 95 percent CI 0.7–2.8). Soft tissue sarcomas (OR = 0.8) and other tumors (OR = 1.1) were not associated with father's smoking. For all cancers combined and acute lymphocytic leukemia, the associations with father's smoking actually decreased slightly with an increasing number of cigarettes smoked (table 3).

Table 4 presents crude odds ratios for children prenatally exposed to smoking by

TABLE 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between mother's cigarette smoking and childhood cancer, Denver, 1976–1983

	Mother's smoking during 3 months prior to conception				Mother's smoking during first trimester of pregnancy				Mother's smoking during three trimesters of pregnancy			
	E+*	E−†	OR	95% CI	E+*	E−†	OR	95% CI	E+*	E−†	OR	95% CI
Controls	65	86	1.0		44	86	1.0		41	86	1.0	
All cancers, by no. of cigarettes/day	80	82	1.3	0.8–2.0	65	82	1.5	1.0–2.5	56	82	1.4	0.9–2.4
1–10	32	82	1.3	0.7–2.4	23	82	1.3	0.7–2.7	22	82	1.4	0.7–2.7
11+	48	82	1.3	0.8–2.2	42	82	1.7	1.0–3.0	34	82	1.5	0.8–2.7
Acute lymphocytic leukemia, by no. of cigarettes/day	24	15	2.1	1.0–4.3	18	15	2.3	1.1–5.0	18	15	2.5	1.2–5.4
1–10	9	15	2.0	0.8–5.0	6	15	1.9	0.7–5.6	6	15	2.0	0.7–5.9
11+	15	15	2.2	1.0–4.9	12	15	2.6	1.1–6.3	12	15	2.9	1.2–6.8
Other leukemias	4	7	0.8	0.2–2.7	4	7	1.1	0.3–4.0	2	7	0.6	0.1–3.0
Lymphoma	10	7	1.9	0.7–5.2	9	7	2.5	0.9–7.0	9	7	2.7	1.0–7.6
Brain cancer	11	16	0.9	0.4–2.1	8	16	1.0	0.4–2.5	6	16	0.8	0.3–2.2
Soft tissue sarcoma	10	11	1.2	0.5–3.0	7	11	1.2	0.5–3.4	7	11	1.3	0.5–3.7
Other tumors	21	26	1.1	0.6–2.1	19	26	1.4	0.7–2.9	14	26	1.1	0.5–2.4

* E+, exposure to mother's cigarette smoking.
† E−, no exposure to smoking by parents and other household members before and after birth.

TABLE 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between father's tobacco smoking and childhood cancer, Denver, 1976–1983

	E+*	E−†	OR	95% CI
Controls	98	86	1.0	
All cancers, by no. of cigarettes/day	122	82	1.3	0.9–2.0
1–10	23	82	1.9	0.9–3.9
11–20	48	82	1.3	0.8–2.1
21+	35	82	1.0	0.6–1.8
Acute lymphocytic leukemia, by no. of cigarettes/day	32	15	1.9	1.0–3.7
1–10	6	15	2.6	0.9–7.9
11–20	11	15	1.6	0.7–3.7
21+	10	15	1.6	0.7–4.0
Other leukemias	6	7	0.8	0.2–2.3
Lymphoma	15	7	1.9	0.7–4.8
Brain cancer	26	16	1.4	0.7–2.8
Soft tissue sarcoma	10	11	0.8	0.3–2.0
Other tumors	33	26	1.1	0.6–2.0

* E+, exposure to father's tobacco smoking (cigarettes, cigars or pipe) during the 12 months prior to birth.
† E−, no exposure to smoking by parents and other household members before and after birth.

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TABLE 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between parents' smoking and childhood cancer, Denver, 1976–1983

	Mother's cigarette smoking in the absence of father's smoking*		Father's tobacco smoking in the absence of mother's smoking†		Mother's and father's smoking‡	
	OR	95% CI	OR	95% CI	OR	95% CI
All cancers	1.7	0.7–4.3	1.4	0.9–2.3	1.5	0.9–2.6
Acute lymphocytic leukemia	2.9	0.8–10.3	1.7	0.7–3.8	2.2	1.0–5.0
Other leukemias	1.5	0.2–14.0	0.8	0.2–3.3	1.0	0.2–4.2
Lymphoma	3.1	0.6–16.2	1.9	0.6–5.7	2.4	0.8–7.2
Brain cancer	§		1.9	0.9–4.2	1.2	0.5–3.0
Soft tissue sarcoma	2.0	0.4–10.2	0.7	0.2–2.3	1.1	0.4–3.4
Other tumors	1.7	0.5–5.9	1.3	0.6–2.5	1.4	0.7–2.9

* Exposure to mother's smoking during the first trimester of pregnancy (13 exposed cancer cases, 8 exposed controls).

† Exposure to father's smoking during the year prior to the child's birth, in the absence of mother's smoking (60 exposed cancer cases, 45 exposed controls).

‡ Exposure to mother's smoking (first trimester) and father's smoking (year prior to child's birth) (52 exposed cancer cases, 36 exposed controls).

§ 0 exposed cases, 8 exposed controls.

either parent alone and by both parents. Independent associations with both mother's and father's smoking were found for all cancers combined, acute lymphocytic leukemia, and lymphomas. Associations with exposure to mother's smoking alone tended to be stronger than those with father's smoking alone, although the risk estimates for mother's smoking were highly imprecise, due to the small number of children exposed to mother's smoking only. Crude associations with prenatal exposure to smoking by both parents exceeded those observed for smoking by the father alone, but were lower than the odds ratios associated with mother's smoking alone. **For prenatal exposure to both mother's and father's smoking, odds ratios were 1.5 (95 percent CI 0.9–2.6) for all cancers combined, 2.2 (95 percent CI 1.0–5.0) for acute lymphocytic leukemia, and 2.4 (95 percent CI 0.8–7.2) for lymphomas. For children exposed to father's smoking only before birth, an odds ratio of 1.9 (95 percent CI 0.9–4.2) was observed for brain cancer** (table 4). However, prenatal exposure to both mother's and father's smoking was not associated with brain cancer (OR = 1.2, 95 percent CI 0.5–3.0).

To take into account differences between cases and controls, analyses were performed with stratification by child's sex, year of birth, age at diagnosis, mother's race, father's education, per capita family income, prior miscarriage, fetal x-rays, mother's alcohol consumption during pregnancy, father's alcohol consumption during the year prior to the child's birth, mother's illnesses and medications taken during pregnancy, and exposure to electromagnetic fields at the time of diagnosis.

Individual adjustment for these variables provided evidence against confouding of either or both parents' smoking, with the exception of father's education. Adjustment for father's education reduced the odds ratios across all diagnostic subgroups, suggesting some confounding of the unadjusted estimates (table 5). Examination of stratum-specific odds ratios also provided some evidence for a modifying effect of father's education on the association between prenatal exposure to smoking and childhood cancer. For all cancers combined, acute lymphocytic leukemia, and brain cancer, enhanced associations were noted among children from more educated families, although the stratum-specific risk estimates were imprecise. Because 80 percent of the nonwhite children (n = 52) were from less educated families, stratified analyses by father's education were also performed restricted to whites only. The same pattern of effect modification was found (not shown).

Our data also suggested effect modifica-

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TABLE 5. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between parents' smoking and childhood cancer, with odds ratios adjusted for father's education, Denver, 1976–1983

	Mother's smoking*		Father's smoking†		Mother's and father's smoking‡	
	OR	95% CI	OR	95% CI	OR	95% CI
All cancers	1.3	0.7–2.1	1.2	0.8–2.1	1.2	0.7–2.1
Acute lymphocytic leukemia	1.9	0.9–4.1	1.4	0.6–3.1	1.8	0.8–4.0
Lymphoma	2.3	0.8–7.1	1.6	0.5–5.4	2.1	0.6–7.3
Brain cancer	0.7	0.3–1.7	1.6	0.7–3.5	0.8	0.3–2.1

* Exposure to mother's cigarette smoking during the first trimester of pregnancy.
† Exposure to father's tobacco smoking during year prior to birth, in the absence of mother's smoking.
‡ Exposure to mother's cigarette smoking during the first trimester and father's tobacco smoking during year prior to child's birth.

tion by the child's sex. For prenatal exposure to both mother's and father's smoking, enhanced risks were observed among male children compared with female children for all cancers combined (OR = 1.8 for males, OR = 1.2 for females) and for acute lymphocytic leukemia (OR = 2.7 for males, OR = 1.7 for females). For brain cancer, an association was found among male children (OR = 2.2), but not females (OR = 0.8). Associations with father's smoking (in the absence of mother's smoking) were observed for male children only, with odds ratios of 2.1 for all cancers combined, 2.8 for acute lymphocytic leukemia, and 4.9 for brain cancer. For female children, odds ratios were 0.8 for each of these diagnostic groups. In contrast, odds ratios for lymphomas associated with mother's and father's smoking were higher among female children than male children.

DISCUSSION

Our findings provide additional evidence that prenatal exposure to cigarette smoking may be a risk factor for cancer in children. In this analysis, prenatal exposure to parents' smoking was associated with an increased risk of all cancers combined, acute lymphocytic leukemia, and lymphoma. For brain cancer, an association was only found for father's smoking in the absence of mother's smoking. Associations tended to be slightly stronger among children from families of higher education and among male children.

The possibility of both systematic and random error needs to be addressed in interpreting these results. Response rates were not optimal, particularly among controls. Although smokers may very well have been less likely to participate than nonsmokers, the results would be invalid only if the magnitude of this tendency differed for cases and controls (35), i.e., if case parents who smoked were more likely to respond than control parents who smoked. Furthermore, adjustment for markers of social class would require this differential nonresponse to operate within social class strata to bias the results. Nonetheless, no data from nonrespondents were available to directly address this possibility and the interpretation of results should be tempered by this concern.

In contrast to other reports (36), in this study, controls, who were selected through random digit dialing, came from more educated families than did cases. This may be due to a lower response among controls from less educated families rather than to a bias in telephone coverage, which has been shown to be adequate in urban areas (37).

Information on smoking status of parents and other household members was based on self-report, generally by the child's mother, and could not be validated. If case mothers were more likely to overreport or underreport smoking during pregnancy, one would expect to see this bias across all diagnostic subgroups. The apparent specificity of the observed associations suggests that recall bias alone is unlikely to account for the observed elevations in risk. On the other

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hand, if all case and control mothers underreported smoking during pregnancy, exposure misclassification would tend to bias the odds ratios toward the null.

Adjustment for confounding variables did not substantially alter the crude odds ratios. It is always possible that the effect of some unmeasured risk factor was not considered. However, it would have to be very strong to account for the observed associations. The virtual absence of identical strong risk factors for specific childhood cancer types (36) argues against that possibility.

Finally, the imprecision in the odds ratios implies that the true magnitudes of association may be markedly greater or less than the point estimates that were observed. Future studies need to overcome the logistical difficulties of identifying adequate numbers of cases for these rare diseases.

Our findings are consistent with several other reports. Associations of mother's cigarette smoking during pregnancy with leukemia (9) and acute lymphocytic leukemia (11) have previously been reported, though the evidence is not consistent (12, 15, 17, 18). The observed increased risk for lymphomas is consistent with associations reported for non-Hodgkin's lymphoma (11), although two studies found no association with non-Hodgkin's lymphoma (18) and lymphoma (17). In this study, brain cancer was not associated with maternal smoking during pregnancy, which is consistent with previous reports (9, 11, 13, 17, 21). Based on a small sample size, a fivefold increase in the risk of brain cancer was reported by Gold et al. (10). In a study of adult cancer and exposure to parental cigarette smoking before age 10 years, Sandler et al. (38) observed no association between mother's smoking and most tumor sites, with the exception of leukemia and lymphoma (OR = 2.7, 95 percent CI 1.3–5.8). An established biologic mechanism for transplacental carcinogenesis enhances the likelihood that these findings pertaining to maternal smoking may represent an etiologic association.

There are few previous reports on the risk of childhood cancer associated with paternal smoking. For father's smoking in the absence of mother's smoking, we found modest increases in the odds ratios for all cancers combined, acute lymphocytic leukemia, and lymphoma. An association with father's smoking in the absence of mother's smoking was also noted for brain cancer. However, for prenatal exposure to both mother's and father's smoking, there was no association with brain cancer. Preston-Martin et al. (13) reported an odds ratio of 1.5 for mothers who lived with a smoker during pregnancy, whereas no association with maternal smoking during pregnancy was found, which is consistent with our results. In contrast, Howe et al. (21) reported no association of brain cancer with paternal smoking during pregnancy. Sandler et al. (38) found excess brain cancers among adults to be associated with childhood exposure to father's smoking, whereas there was no association with exposure to mother's smoking. Although there are theoretical biologic mechanisms linking paternal exposure to cancer risk in the offspring through genetic mutations, empirical evidence in support of this process is limited.

In this analysis, we compared cases and controls with prenatal exposure to smoking to children without exposure to smoking by parents and other household members during the prenatal and postnatal period. Previous studies may have underestimated the risk of childhood cancer associated with prenatal exposure to cigarette smoking due to potential misclassification of children exposed to father's smoking as unexposed. If father's smoking is an independent risk factor for childhood cancer, misclassification of children with exposure to paternal smoking as "unexposed" would tend to underestimate the true association with maternal smoking. The questionnaire in the present study did not elicit any information on maternal exposure to cigarette smoke outside the home. It is therefore possible that some children classified in this analysis as unexposed were actually passively exposed outside the home. It is, however, unlikely that such exposure misclassification is differen-

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tially distributed among cases and controls, so it would bias the risk estimates toward the null.

In our data, adjustment for father's education slightly reduced the odds ratios for both maternal and paternal smoking. There was also some indication of effect modification, with stronger associations observed among children from more educated families, but there is little basis for arguing that this reflects a true interaction rather than random error.

In this analysis, there also appeared to be effect modification for the child's sex. A greater risk of cancer associated with prenatal exposure to cigarette smoke was found for male children. There is some evidence that prenatal exposures may affect male and female fetuses differently. A stronger association of maternal smoking during pregnancy on proportional reduction in birth weight and length among male infants compared with female infants has been reported (39). Male infants have also been reported to have greater reductions in birth weight in relation to maternal alcohol consumption (40). This study provides some evidence for an analogous effect of smoking on childhood cancer among male versus female offspring.

The major difficulty in interpreting the results with regard to source of exposure is that most children prenatally exposed to mother's smoking were also exposed to father's smoking. Although the number of children exposed to either parent's smoking alone was small, our data suggested that both sources of exposure may be independent risk factors. The interpretation of the results is further complicated by the fact that most parents who smoked before the child's conception continued to smoke during pregnancy and after the child's birth. Children who were transplacentally exposed to parents' tobacco smoking therefore become passive smokers after birth.

Maternal smoking is among the most prevalent potentially harmful exposures during pregnancy and remains a significant public health concern (41). Given the prevalence of maternal smoking among controls, the estimated relative risks for first trimester smoking obtained in this study, and the assumption that the associations are causal, it is estimated that 6 percent of all childhood cancers and 17 percent of acute lymphocytic leukemias might be attributable to this exposure. However, the risk estimates from our study are limited due to small numbers. Further studies that use larger case groups of specific cancers (acute lymphocytic leukemia, lymphoma, and brain cancer) and that consider the independent effects of prenatal exposure to maternal and paternal smoking, as well as passive smoking in early childhood, are therefore warranted.

REFERENCES

1. US Public Health Service. The health consequences of smoking for women: a report of the Surgeon General. US Department of Health and Human Services, Office on Smoking and Health. Washington DC: US GPO, 1983.
2. Christianson RE. Gross differences observed in the placentas of smokers and nonsmokers. Am J Epidemiol 1979;110:178–87.
3. Van Vunakis H, Longone JJ, Milunsky A. Nicotine and cotinine in the amniotic fluid of smokers in the second trimester of pregnancy. Am J Obstet Gynecol 1974;120:64–6.
4. Andresen BD, Ng KJ, Iams JD, et al. Cotinine in amniotic fluids from passive smokers. (Letter.) Lancet 1982;1:791–2.
5. Smith N, Austen J, Rolles CJ. Tertiary smoking by the fetus (Letter.) Lancet 1982;1:1252–3.
6. Bottoms SF, Kuhnert BR, Kuhnert PM, et al. Maternal passive smoking and fetal serum thiocyanate levels. Am J Obstet Gynecol 1982;144: 787–91.
7. Hauth JC, Hauth J, Drawbaugh RB, et al. Passive smoking and thiocyanate concentrations in pregnant women and newborns. Obstet Gynecol 1984;63:519–22.
8. Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. Br Med J 1958;1:1495–1508.
9. Neutel CI, Buck C. Effect of smoking during pregnancy on the risk of cancer in children. JNCI 1971;47:59–63.
10. Gold E, Gordis L, Tonascia J, et al. Risk factors for brain tumors in children. Am J Epidemiol 1979;109:309–19.
11. Stjernfeldt M, Berglund K, Lindsten J, et al. Maternal smoking during pregnancy and risk of childhood cancer. Lancet 1986;1:1350–2.
12. Manning MD, Carroll BE. Some epidemiological aspects of leukemia in children. JNCI 1957; 19:1087–94.
13. Preston-Martin S, Yu MC, Benton B, et al. N-Nitroso compounds and childhood brain tumors:

2023382091

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a case-control study. Cancer Res 1982;42:5240–5.
14. Grufferman S, Wang HH, DeLong ER, et al. Environmental factors in the etiology of rhabdomyosarcoma in childhood. JNCI 1982;68:107–13.
15. Van Steensel-Moll HA, Valkenburg HA, Vandenbroucke JP, et al. Are maternal fertility problems related to childhood leukaemia? Int J Epidemiol 1985;14:555–9.
16. Johnston HE, Mann JR, Williams J, et al. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC): case-control study in children with germ cell tumours. Carcinogenesis 1986;7:717–22.
17. McKinney PA, Stiller CA. Maternal smoking during pregnancy and the risk of childhood cancer. (Letter.) Lancet 1986;2:519.
18. Buckley JD, Hobbie WL, Ruccione K, et al. Maternal smoking during pregnancy and the risk of childhood cancer. (Letter.) Lancet 1986;2:519–20.
19. Bunin GR, Kramer S, Marrero O, et al. Gestational risk factors for Wilms' tumor: results of a case-control study. Cancer Res 1987;47:2972–7.
20. Kramer S, Ward E, Meadows AT, et al. Medical and drug risk factors associated with neuroblastoma: a case-control study. JNCI 1987;78:797–804.
21. Howe GR, Burch JD, Chiarelli AM, et al. An exploratory case-control study of brain tumors in children. Cancer Res 1989;49:4349–52.
22. Resnik-Schuller H. Comparative perinatal carcinogenesis. Boca Raton, FL: CRC Press, 1984.
23. Nicolov IG, Chernozemsky IN. Tumors and hyperplastic lesions in Syrian hamsters following transplacental and neonatal treatment with cigarette smoke condensate. J Cancer Res Clin Oncol 1979;94:249–56.
24. Grufferman S, Delzell ES, Maile MC, et al. Parents' cigarette smoking and childhood cancer. Med Hypotheses 1983;12:17–20.
25. McKinney PA, Cartwright RA, Saiu JM, et al. The inter-regional epidemiological study of childhood cancer (IRESCC): a case-control study of aetiological factors in leukaemia and lymphoma. Arch Dis Child 1987;62:279–87.
26. Tomatis L, Cabral JR, Likhachev AJ, et al. Increased cancer incidence in the progeny of male rats exposed to ethylnitrosourea before mating. Int J Cancer 1981;28:475–8.
27. Bridges BA, Clemmesen J, Sugimura T. Cigarette smoking—Does it carry a genetic risk? Mutat Res 1979;65:71–81.
28. Prager K, Malin H, Spiegler D, et al. Smoking and drinking behavior before and during pregnancy of married mothers of live-born infants and stillborn infants. Public Health Rep 1984;99:117–27.
29. Friedman GD, Pettiti DB, Bawol RD. Prevalence and correlates of passive smoking. Am J Public Health 1983;73:401–5.
30. Savitz DA, Wachtel H, Barnes FA, et al. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. Am J Epidemiol 1988;128:21–38.
31. Savitz DA, Zuckerman DL. Childhood cancer in the Denver metropolitan area 1976-1983. Cancer 1987;59:1539–42.
32. Brookmeyer R, Liang KY, Linet M. Matched case-control designs and overmatched analyses. Am J Epidemiol 1986;124:693–701.
33. Miettinen OS. Estimability and estimation in case-referent studies. Am J Epidemiol 1976;103:226–35.
34. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. JNCI 1959;22:719–48.
35. Hartge P, Brinton LA, Rosenthal JF, et al. Random digit dialing in selecting a population-based control group. Am J Epidemiol 1984;120:825–33.
36. Greenberg RS, Shuster JL Jr. Epidemiology of cancer in children. Epidemiol Rev 1985;7:22–48.
37. Greenland S, Criqui MH. Are case-control studies more vulnerable to response bias? Am J Epidemiol 1981;114:175–7.
38. Sandler DP, Everson RB, Wilcox AJ, et al. Cancer risk in adulthood from early life exposure to parents' smoking. Am J Public Health 1985;75:487–92.
39. Wertelecki W, Hoff C, Zansky S. Maternal smoking: greater effect on males, fetal tobacco syndrome? Teratology 1987;35:317–20.
40. Little RE, Asker RL, Sampson PD, et al. Fetal growth and moderate drinking in early pregnancy. Am J Epidemiol 1986;123:270–8.
41. Werler MM, Pober BR, Holmes LB. Smoking and pregnancy. Teratology 1985;32:473–81.

2023382092

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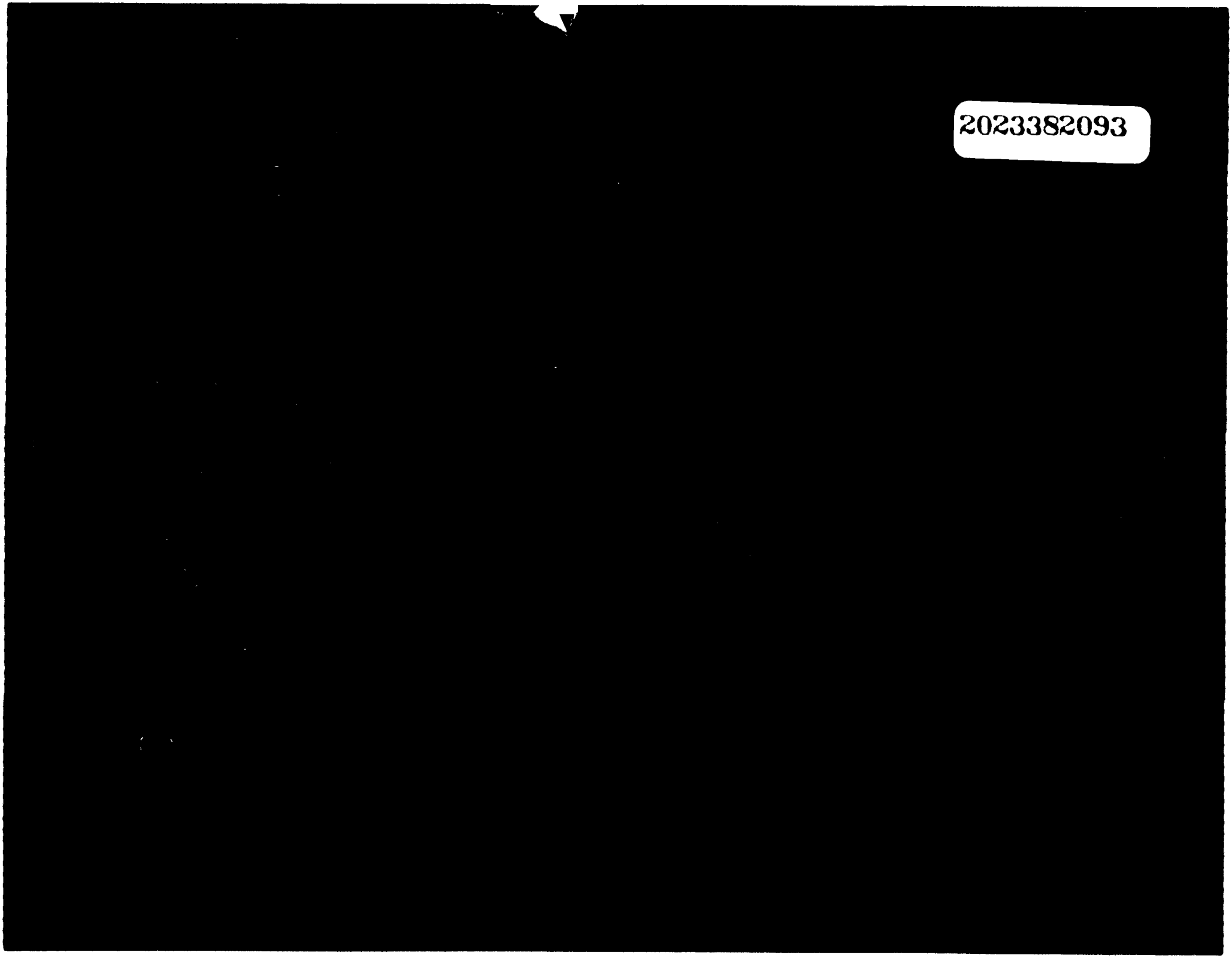

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